



# Gene Therapy: Cure or Poison? The Proper Role of the FDA in the Bubble Boy Disease Question

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# GENE THERAPY: CURE OR POISON?

## *The Proper Role of the FDA in the Bubble Boy Disease Question*

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Submitted May 24, 2004*

this paper is submitted to satisfy the course requirement and the written requirement.

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## ABSTRACT

On January 14, 2003, the Food and Drug Administration “suspended 27 gene therapy trials involving several hundred patients after learning that a second child treated in France had developed a condition resembling leukemia.”<sup>1</sup> Gene therapy treats diseases caused by defective genes by introducing healthy genes into the body. For patients who are battling life-threatening diseases, the only chance of survival may be the hope of gene therapy, perhaps because there is no known cure, no available matched transplant donor, or no cures without even worse side effects. “Some of the trials being halted are intended to treat AIDS and cancer.”<sup>2</sup> The “second child treated in France,” who caused the alarm, had received gene therapy treatment not for AIDS or cancer, but for the less common ailment “bubble boy disease,” a severe and fatal immunodeficiency disorder. Bubble boy disease attacks newborn boys, who while in the womb, relied on their mother’s immunity but, once born, are left helpless in fighting other diseases that attack their infant bodies. With the trials halted, parents are left helpless to seek gene therapy for their children. Is it right to eliminate alternate, but risky remedies?

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<sup>1</sup>Andrew Pollack, “Gene Therapy Trials Halted,” THE NEW YORK TIMES, January 15, 2003 at Health and at <http://www.newyorktimes.com/2003/01/15/health/15GENE.html>.

<sup>2</sup>*Id.*

# I. INTRODUCTION

What is “bubble boy disease?” Bubble boy disease is the popular term for a condition that leaves a male child without a working immune system. The child can rely on the immunity transferred to him from his mother while in the womb, but once born, the immunity promptly wears off, leaving the child helpless against disease. Although other immunodeficiency disorders as acquired immunodeficiency syndrome (“AIDS”)<sup>3</sup> may be more notorious, bubble boys are fighting the same deadly handicap. Since the child cannot depend on a normal, healthy immune system to fight off diseases, a common cold can quickly worsen into pneumonia and be deadly. “Without an immune system, a patient is completely vulnerable to infection a pathogen that would be harmless to a person with normal immunity would destroy a SCID patient.”<sup>4</sup> Unfortunately, unlike AIDS, there is no way to prevent this genetic disease, and left untreated, death is certain within two years.<sup>5</sup> Thus, it was the custom to isolate bubble boy patients in a plastic bubble to keep out germs.

Who are these bubble boys? Bubble boy disease is extremely rare, affecting only 0.001 percent of children at birth.<sup>6</sup> Yet it is a death sentence without explanation. The only available treatment for these boys is

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<sup>3</sup>This paper uses numerous acronyms. Although these acronyms are defined repeatedly throughout the paper, a list of acronyms used is attached at the end of this paper.

<sup>4</sup>“Early Marrow Transplant May be Key to ‘Bubble Boy’ Disease Cure,” DOCTOR’S GUIDE, May 5, 1997 at <http://www.pslgroup.com/dg/25666.htm>.

<sup>5</sup>“FDA Places Temporary Halt on Gene Therapy Trials Using Retroviral Vectors in Blood Stem Cells,” FDA TALK PAPER, January 14, 2003 at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01190.html> (“Infants with X-SCID have a gene defect that leads to a complete lack of white blood cells that can fight infection. Without treatment, they die from complications of infectious diseases during the first year of life.”).

<sup>6</sup>“Homo Sapiens Diseases Immunity,” MOLECULAR IMMUNOLOGY at <http://xoomer.virgilio.it/medicine/pathohomotissueimmunity.html> (“severe combined immunodeficiency (SCID) / Swiss type agammaglobulinemia / ‘bubble boy disease / syndrome’ Epidemiology : 1 in 75,000 live births (1 in 100,000 live male births).”). *See also* “New Cure For Bubble Boy Disease,” CBS NEWS, April 17, 2002 at <http://www.cbsnews.com/stories/2002/04/17/tech/main506451.shtml> (“The five French boys were born with severe combined immunodeficiency, or SCID, an inherited disease that occurs in about 1 in 75,000 births.”).

bone marrow transplants.<sup>7</sup> Transplants require finding a matched and willing donor.<sup>8</sup> Transplants have the dangers associated with any surgical procedure.<sup>9</sup> Transplants come with the deadly risk of incurring another fatal disease, graft versus host disease (“GVHD”), a condition caused if the body reacts negatively to the new transplant.<sup>10</sup>

While bone marrow transplants are the only *available* treatments, they are not the only *known* treatments.

In 2000, a miraculous new treatment using gene therapy, which is a method of treating genetic diseases by introducing healthy genes into the body, cured bubble boy disease for the first time.<sup>11</sup> Gene therapy

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<sup>7</sup>“FDA Places Temporary Halt on Gene Therapy Trials Using Retroviral Vectors in Blood Stem Cells,” FDA TALK PAPER, January 14, 2003 at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01190.html> (“The only treatment for this condition is a bone marrow transplant.”). *See also* “Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrows.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrows.org/MEDICAL/immune_sys_disorders.html) (“For almost all congenital immune system disorders, however, the treatment of choice is a blood stem cell transplant.”).

<sup>8</sup>“Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrows.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrows.org/MEDICAL/immune_sys_disorders.html) (“The main obstacle to a blood stem cell transplant is lack of a matching donor. Doctors first look for donors in a patient’s family, but only about one in four patients find a match in their own family.”). *But see* “Early Marrow Transplant May be Key to ‘Bubble Boy’ Disease Cure,” DOCTOR’S GUIDE, May 5, 1997 at <http://www.pslgroup.com/dg/25666.htm> (“They also have learned that these children need not have a perfectly matched donor, but can use a parent’s ‘half-matched’ marrow.... ‘Until 1982, SCID was invariably fatal unless the patient had a brother or sister who was an exact match to donate bone marrow,’ [Rebecca] Buckley [chief of Duke’s division of pediatric allergy and immunology] explained. ‘What we see now is that a sibling match isn’t necessary; haploidentical parental marrow will work, too.’ A haploid match is a half match.”).

<sup>9</sup>However, bubble boys no longer endure difficult pre-transplant treatments to prepare the body for the transplant, including radiation and chemotherapy. *Compare* “Early Marrow Transplant May be Key to ‘Bubble Boy’ Disease Cure,” DOCTOR’S GUIDE, May 5, 1997 at <http://www.pslgroup.com/dg/25666.htm> (“Furthermore, the babies do not need toxic pre-transplant chemotherapy, as is often thought and currently practiced.... [Rebecca] Buckley [chief of Duke’s division of pediatric allergy and immunology] also found that transplants can be done without exposing the infant to toxic chemotherapy, which can have life-long repercussions. Many doctors give chemotherapy to all bone marrow transplant patients because they are following standard cancer treatment protocol, Buckley said. But chemotherapy is not necessary in children with SCID because they have no T-cells to attack and destroy the foreign donor marrow, as is the case with cancer patients. ‘Patients with SCID have no immune systems to reject the transplants. Our approach avoids toxic agents and their possible complications,’ she said.”) *with* “Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrows.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrows.org/MEDICAL/immune_sys_disorders.html) (“To prepare for a stem cell transplant, patients receive high doses of chemotherapy and/or radiation therapy to destroy their immune systems... . The pre-transplant treatment can be very hard on a patient’s body, and there is a risk of organ damage, including permanent sterility.”).

<sup>10</sup>“Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrows.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrows.org/MEDICAL/immune_sys_disorders.html) (“In addition, the donated stem cells might attack the patient’s body. This is called graft-versus-host disease (GVHD). If GVHD develops, doctors can treat it with drugs, but GVHD still sometimes causes death after a stem cell transplant.”). *But see* “Early Marrow Transplant May be Key to ‘Bubble Boy’ Disease Cure,” DOCTOR’S GUIDE, May 5, 1997 at <http://www.pslgroup.com/dg/25666.htm> (“Moreover, [Rebecca] Buckley [chief of Duke’s division of pediatric allergy and immunology] has found a way to reduce a potentially fatal complication of transplants called graft-versus-host disease (GVHD). By removing the donor’s T-cells before the transplant, the donor’s marrow cannot rise up and attack the patient’s vital organs – a common complication with bone marrow transplants. And, by removing these cells before the transplant, the infant avoids the toxic drugs normally given to suppress the donor’s T-cells.”).

<sup>11</sup>*See* “Gene Therapy Cures ‘Bubble Boy,’” NEW SCIENTIST, April 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992124> (“Alain Fischer’s team at the Necker Hospital in Paris re-

treatments of bubble boy disease promised almost perfect success rates, did not require any donor, and did not come with the threat of a negative reaction to the treatment.<sup>12</sup>

However, there is a one in a hundred-thousand chance that any one transferred gene will integrate in the gene that causes leukemia.<sup>13</sup> Moreover, for gene therapy to have a high chance of successfully integrating in the right gene, doctors introduce one million genes into the body.<sup>14</sup> Although it usually takes multiple genetic changes to cause leukemia, the number of genes introduced genes made leukemia a possibility.<sup>15</sup> This concern was only hypothetical until two children developed leukemia-like symptoms after undergoing gene therapy treatment for bubble boy disease.<sup>16</sup> The French, English, and American governments responded to this occurrence and quickly halted the trials.<sup>17</sup> Still, fifteen patients – eleven boys in Paris and four boys in London – were cured of bubble boy disease from gene therapy before the trials were halted.<sup>18</sup> Now, other patients, who were waiting to receive gene therapy treatments, face certain death, because this option is no longer available. The fate of these patients spurs endless questions of public policy, constitutional rights, and ethical dilemmas. This paper uncovers these questions and attempts to answer them in light of the controversial January 14, 2003 decision of the Food and Drug Administration (“FDA”) to suspend

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ported the first-ever treatment in 2000.”).

<sup>12</sup>See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc) (“There will be no more ‘bubble boys.’”).

<sup>13</sup>Andrew Pollack, “2nd Cancer is Attributed to Gene Used in French Test,” THE NEW YORK TIMES, January 17, 2003 at Health and at <http://www.newyorktimes.com/2003/01/17/health/17GENE.html> (“Dr. [Christof] von Kalle [a doctor at the Cincinnati Children’s Hospital Medical Center and a collaborator with the French researchers] said the chance of a virus landing on LMO-2 was about 1 in 100,000.”).

<sup>14</sup>*Id.* (“But since each child was given about one million cells, the probability is very high that a child received at least one cell in which the virus landed on the gene [that causes leukemia].”).

<sup>15</sup>*Id.* (“But Dr. von Kalle said scientists believed that turning on just one oncogene [a cancer-promoting gene] would not be a problem because it usually requires multiple genetic changes to turn a cell cancerous.”).

<sup>16</sup>*Id.* (“In both cases, the gene inserted into the boys’ blood-forming stem cells landed on or near an oncogene, or cancer-promoting gene, called LMO-2, which can spur childhood leukemia. In the first case the gene landed inside LMO-2 and the second landed near enough to turn on the gene, Dr. von Kalle said.”). See also Joshua J. Loomis, “X-SCID Gene Therapy in France – An Undesirable Integration Event,” VIRAL VECTORS AS MEDIATORS OF GENE THERAPY at <http://narnia.n.ml.org/skier/writings/doc/microm%20496.doc> (noting that the LMO-2 gene on chromosome 11 has been linked to leukemia).

<sup>17</sup>Andrew Pollack, “Gene Therapy Trials Halted,” THE NEW YORK TIMES, January 15, 2003 at Health and at <http://www.newyorktimes.com/2003/01/15/health/15GENE.html>.

<sup>18</sup>*Id.*



twenty-seven “gene therapy trials involving several hundred patients.”<sup>19</sup>

The FDA decision to halt the trials clearly prevents more patients from contracting leukemia or another life-threatening ailment through gene therapy treatments. Yet it simultaneously prevents these patients from receiving a cure of different fatal diseases, including bubble boy disease. The governmental decision to halt the trials clearly protects an unaware public from undergoing a dangerous procedure. Yet it simultaneously blocks well-informed parents from choosing the uncertain risks of gene therapy over the certain risks of bubble boy disease for their beloved children. The governmental decree rescues parents from making very difficult decisions. Yet it robs them of their right, perhaps a constitutional right, to make those decisions.

The government’s growing paternal virtues may be a direct result of the American people hastily reacting in anger, disappointment, and shock whenever a rare but highly publicized failure, especially one that results in death, hits the news stands. The result for the American public is often the sought-after higher standards of safety, but those higher standards mean fewer available choices. Less choice is sometimes better; the public does not always have the resources to make risk-benefit decisions for everyday incidents. Perhaps, this cycle is useful in the majority of the FDA decisions covering everyday resolutions on food labeling, nonprescription drugs, and truthful advertising.

However, bubble boy disease is far from an everyday incident, and the FDA decision is hardly an everyday resolution. This paper analyzes whether the proper role of the FDA should be different in rare life-threatening situations than in everyday situations. In cases of uncommon fatal diseases, this paper determines that the FDA should adopt less rigid regulations, allow for more personal autonomy, and grant alternative treatment

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<sup>19</sup>*Id.*

options despite a higher risk level involved. A governmental tolerance for high-risk treatments in cases of rare fatal diseases actually makes legal, financial, and ethical sense. Legally, this paper asserts that the United States Constitution gives a dying person the right to choose a risky treatment that offers the only chance at survival. Financially, a person suffering from a rare disease is more likely to dedicate proportionally more resources to the disease than the public. Ethically, the individual who will die if left untreated deserves the opportunity of treatment, despite its risks, though the public would decide against the risk. This paper discusses each of these reasons in detail below.

The United States Constitution limits the authority of the federal government in favor of individual power on issues of privacy, self-dignity, and personal autonomy. For example, the famous case of *Roe v. Wade*<sup>20</sup> stands for upholding rights to autonomy and privacy in making decisions over one's body, following the paths carved from *Griswold v. Connecticut*<sup>21</sup> and *Eisenstadt v. Baird*.<sup>22</sup> The well-known case of *Cruzan v. Director, Missouri Dep't of Health*<sup>23</sup> held that every person has constitutional rights to life and dignity in death. Finally, *Maher v. Roe*<sup>24</sup> represents a case where the United States Supreme Court found a right to medical treatment. These significant constitutional cases represent individual rights, religious and philosophical rights, and medical rights that state personhood, self-dignity, and life are critical considerations under the U.S. Constitution.

Similar discussions surface in cases against the FDA specifically dealing with rare fatal diseases. For example, during the AIDS revolution, AIDS patients fought for investigational new drugs ("IND"), which are usually limited to clinical studies, to be available to non-clinical participants as treatment under certain

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<sup>20</sup>*Roe v. Wade*, 410 U.S. 113 (1973).

<sup>21</sup>*Griswold v. Connecticut*, 381 U.S. 479 (1965).

<sup>22</sup>*Eisenstadt v. Baird*, 405 U.S. 438 (1972).

<sup>23</sup>*Cruzan v. Director, Missouri Dep't of Health*, 497 U.S. 261 (1990).

<sup>24</sup>*Maher v. Roe*, 432 U.S. 464 (1977).

conditions.<sup>25</sup> Cancer patients also fought these fights, arguing that their constitutional rights of privacy protected their right to use available, albeit not approved, drugs to treat their disease.<sup>26</sup> On appeal, the Tenth Circuit agreed and acknowledged the special case of these patients. The Tenth Circuit asked, “[W]hat can ‘generally recognized’ as ‘safe and effective’ mean as to such persons who are so fatally stricken with a disease for which there is no known cure?”<sup>27</sup> Admittedly, the law does not always side with this view, and the Supreme Court unanimously reversed this decision by the Tenth Circuit, finding that there is “no special provision for drugs used to treat terminally ill patients.”<sup>28</sup> Nonetheless, the continuing AIDS and cancer fights maintain that constitutional rights of privacy, self-dignity, and autonomy should allow patients of rare, fatal diseases to choose more dangerous, and less certain treatments.<sup>29</sup> This paper argues that these same rights extend to riskier gene therapy treatments, as well.<sup>30</sup> If there is not an available transplant-donor match, a child inflicted with bubble boy disease will die. In that case, the United States Constitution and common law guarantees that boy an autonomous right to make his personal and private decision among all known treatments, regardless of risk, to best maintain his dignity and treasure his life.

Second, there is the practical consideration of limited resources. With everyday products, the public consumption is widespread, and thus the FDA will concentrate its efforts on those issues. Correspondingly,

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<sup>25</sup>42 U.S.C. § 300cc-12 (requiring the FDA to encourage sponsors of clinical trials to make AIDS drugs available for treatment purposes if there is preliminary evidence that the drug prevents or treats AIDS). *See also* Peter B. Hutt and Richard A. Merrill, “The AIDS Revolution,” *FOOD AND DRUG LAW: CASES AND MATERIALS*, Westbury, NY: The Foundation Press Inc (1991) at 552 (discussing the “revolution in the availability of investigational drugs to treat life-threatening diseases, in the early approval of new drugs for these diseases”).

<sup>26</sup>*Rutherford v. United States*, 438 F. Supp. 1287 (W.D. Okl. 1977).

<sup>27</sup>*Rutherford v. United States*, 582 F.2d 1234, 1237 (10th Cir. 1978).

<sup>28</sup>*Rutherford v. United States*, 442 U.S. 544 (1979).

<sup>29</sup>Even the FDA recognized that it must make its decision in light of the fatal results of the disease. *See* “FDA Places Temporary Halt on Gene Therapy Trials Using Retroviral Vectors in Blood Stem Cells,” FDA TALK PAPER, January 14, 2003 at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01190.html> (“FDA’s continuing review of adverse event reports from all U.S. studies involving retroviral vectors has to date found no evidence of leukemia caused by the gene therapy. Moreover, the agency has to consider the potential risks of any experimental therapy within the context of the disease it may treat – in this case a devastating disease in children.”).

<sup>30</sup>When the FDA placed the halt on gene therapy treatments, it made a similar statement, although it has failed to follow through on its promise. *See* “FDA Places Temporary Halt on Gene Therapy Trials Using Retroviral Vectors in Blood Stem Cells,” FDA TALK PAPER, January 14, 2003 at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01190.html> (“FDA will consider and evaluate specific requests for clinical indications for fatal or life-threatening disorders for which there are no viable alternative treatments.”).

the individual will devote few resources to learning more about each of these numerous trivial products. Conversely, for rare diseases, the FDA will devote fewer resources, because it affects a small percentage of the public, but the afflicted individual will concentrate a great amount of resources on the singular and relatively significant disease. Therefore, limited resources dictate that the FDA or another public establishment is probably the best conductor of a risk-benefit analysis in cases of everyday products.<sup>31</sup> Yet the individual is probably the best conductor of risk-benefit analysis in cases of rare fatal diseases. The FDA will proportionally devote fewer resources to bubble boy disease as compared to diseases that affect more children, while the parents of an afflicted child will devote almost a hundred percent of their resources to understanding this disease. In light of this disparity of dedicated resources, the individual in the rare fatal case of bubble boy disease should make the risk-benefit decision regarding gene therapy. Although the risks of gene therapy are high, allowing the individual to make this decision is the most sound approach, with respect to both finances and time, design.

Finally, there is the unduly risk-averse characteristic of public organizations.<sup>32</sup> News media have limited resources of space, time, and money to inquire about current happenings. Consequently, mass media reports failures, catastrophes, and errors more often than consistent performances, expected successes, and unencumbered results. Thus, the public perceives the risk of activities to be greater than in actuality, such as the risks of a plane crashing, beef carrying mad cow disease, and earthquakes striking California.<sup>33</sup> Consequently,

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<sup>31</sup>See “Risk-Benefit Analysis,” WUSTL, October 12, 1994 at [http://capita.wustl.edu/ME567\\_Informatics/concepts/riskben.html](http://capita.wustl.edu/ME567_Informatics/concepts/riskben.html) (“When individuals are exposed to involuntary risk, risk which they have no control, they make risk aversion their primary goal. Under these circumstances individuals require the probability of risk to be as much as one thousand times smaller than for the same situation under their perceived control.”).

<sup>32</sup>See *id.* (“Real future risk as disclosed by the fully matured future circumstances when they develop. Statistical risk, as determined by currently available data, as measured actuarially for insurance premiums. Projected risk, as analytically based on system models structured from historical studies. Perceived risk, as intuitively seen by individuals. Air transportation as an example: Flight insurance company - statistical risk. Passenger - perceived risk. Federal Aviation Administration (FAA) – projected risks.”).

<sup>33</sup>See *id.* (“Real future risk as disclosed by the fully matured future circumstances when they develop. Statistical risk, as determined by currently available data, as measured actuarially for insurance premiums. Projected risk, as analytically based on system models structured from historical studies. Perceived risk, as intuitively seen by individuals. Air transportation as an example: Flight insurance company - statistical risk. Passenger - perceived risk. Federal Aviation Administration (FAA) – projected risks.”).

the public seeks greater insurance against these risks than suitable.<sup>34</sup> As public servants, Congressional representatives vying for reelection respond to these demands by directing administrative regulators, like the FDA, to set higher than necessary standards to avoid these risks. The resultant, unduly risk-averse nature of the FDA is desirable in an everyday setting, where the majority of individuals has risk-adverse preferences and does not want to ascertain the risk for numerous trivial everyday purchases.<sup>35</sup> However, this resultant unduly risk-adverse nature is undesirable in rare fatal situations, where there is a higher chance that the individual will prefer high-risk options, especially when those options offer the only chance for survival. “Doctors at Great Ormond Street say two UK patients have died in 2002, because they did not start gene therapy in time.”<sup>36</sup>

This paper tells the full sad story of children suffering from bubble boy disease, the medical developments of gene therapy, the promising trials that the FDA abruptly halted, and the standard FDA procedures that threaten lives. The first section of the paper introduces the medical developments of bubble boy disease, exposing why the traditional treatment of bone marrow transplants is often impossible, inadequate, or unusually lethal in itself for bubble boy patients. The paper then introduces the history of gene therapy, illustrating the science of gene therapy treatments that use retroviruses, like in the bubble boy treatments, to show why they have a higher risk. It then shares the complete history of the halted trials, from the early successful results to the nervous apprehension after the first boy contracted leukemia to the immediate decision to suspend trials after the second child contracted leukemia.

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<sup>34</sup>See *id.* (“Although many people feel that flying is more risky than driving, statistics show otherwise. Perception of control is a very important factor that explains why voluntary activities have risks of 100 to 1000 times greater than involuntary activities.”).

<sup>35</sup>“The Theory of Risk Aversion,” NEW SCHOOL at <http://cepa.newschool.edu/het/essays/uncert/aversion.htm> (“We first turn to the concept of univariate ‘risk aversion’ which, intuitively, implies that when facing choices with comparable returns, agents tend chose the less-risky alternative, a construction we owe largely to Milton Friedman and Leonard J. Savage (1948).”).

<sup>36</sup>See “‘Miracle’ Gene Therapy Trial Halted,” NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878>.

After giving a vivid picture of the disease, the treatment options, and the FDA decision, the paper then discusses the role of the FDA. The paper introduces the standard procedure of the FDA, and the manner in which the FDA regulates gene therapy. The paper delves into the structure of the FDA, including its relationship with the National Institutes of Health (“NIH”) in regulating bubble boy disease, gene therapy, and clinical trials.

With a complete picture of the disease, the science, the treatment, and the regulator, the paper discusses the legal and social consequences of the FDA decision to halt the gene therapy trials that promised to cure bubble boy disease. On one hand, the FDA has a duty to protect the American people, and faces certain liability for failure to live up to its duty. The American people demand that the FDA use its power to avoid putting the American people in risk of peril. On the other hand, the Constitution upholds privacy, autonomy, and self-dignity. Children suffering from bubble boy disease are facing imminent death unless treated, and gene therapy is sometimes the only chance for life. The parents of these children are willing to devote proportionally more resources to determine the individual risk-benefit analysis for their child. Furthermore, they are in the best position to understand if the risk is not a risk at all, because it has become their last hope. This final section of the paper discusses a way of achieving a proper balance between the two competing and conflicting interests.

## II. THE SCIENCE

### A. The Disease

X-linked severe combined immunodeficiency (“X-SCID”)<sup>37</sup> is the proper medical term, but “bubble boy disease” evokes a remarkably accurate image of the condition afflicting only male children with such severe immune system impairments at birth that they live in a bubble. During pregnancy, SCID infants carry the immunity transferred to them from their mother, but once born, they gradually lose their defense against infection. Without medical intervention, every single child plagued with SCID has an early death sentence. “Most infants with severe combined immunodeficiency disease develop pneumonia, thrush, and diarrhea, usually by age 3 months.”<sup>38</sup> With a malfunctioning immune system, these serious infections progress into conditions that are even more serious. “If not treated, these children usually die before age 2.”<sup>39</sup>

Although it affects only one child in about 75,000 births, SCID appalls parents and doctors alike.<sup>40</sup> “Severe combined immunodeficiency disease is the most serious immunodeficiency disorder. It can be caused by several different genetic defects, most of which are hereditary.”<sup>41</sup> Unfortunately, while scientists understand

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<sup>37</sup>There are many different forms of Severe Combined Immunodeficiency (“SCID”). This paper focuses on X-linked SCID (“X-SCID”), the most common form of SCID, known also as bubble boy disease, because it affects only male children. However, ADA-SCID, which is SCID caused by the absence of the enzyme adenosine deaminase (“ADA”), another known form of SCID, affects both male and female children. In fact, ADA-SCID, although less famous, was identified much sooner, and was understood almost immediately to be single-gene defect, which is easier to treat. Thus, treatments were available for ADA-SCID before the causes of X-SCID were known. Indeed, at that time, X-SCID had not even been identified. This paper uses the terms “X-SCID” and “bubble boy disease” interchangeably. This paper uses the term “SCID” to include all forms of SCID. When referring to other forms of SCID, this paper identifies it with a different prefix, such as “ADA-SCID.”

<sup>38</sup>“Severe Combined Immunodeficiency Disease,” THE MERCK MANUAL – SECOND HOME EDITION at <http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.

<sup>39</sup>“Severe Combined Immunodeficiency Disease,” THE MERCK MANUAL – SECOND HOME EDITION at <http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.

<sup>40</sup>“Homo Sapiens Diseases Immunity,” MOLECULAR IMMUNOLOGY at <http://xoomer.virgilio.it/medicine/pathohomotissueimmunity.html> (“severe combined immunodeficiency (SCID) / Swiss type agammaglobulinemia / “bubble boy disease / syndrome” Epidemiology : 1 in 75,000 live births (1 in 100,000 live male births)”). See also “New Cure For Bubble Boy Disease,” CBS NEWS, April 17, 2002 at <http://www.cbsnews.com/stories/2002/04/17/tech/main506451.shtml> (“The five French boys were born with severe combined immunodeficiency, or SCID, an inherited disease that occurs in about 1 in 75,000 births.”).

<sup>41</sup>“Severe Combined Immunodeficiency Disease,” THE MERCK MANUAL – SECOND HOME EDITION at

some of the diverse genetic origins of SCID well, other causes of SCID remain inexplicable. “The most common type is linked to the X chromosome, making this form affect only males. Other forms of SCID usually follow an autosomal recessive inheritance pattern or are the result of spontaneous mutations. One of these other forms is linked to a deficiency of the enzyme adenosine deaminase (ADA). Other cases of SCID are caused by a variety of other defects.”<sup>42</sup>

X-SCID or bubble boy disease is the most common form of SCID, but scientists identified ADA-SCID in the 1970s, much earlier than X-SCID.<sup>43</sup> ADA-SCID was recognized as a single-gene defect immediately.<sup>44</sup> Long before cloning and sequencing the gene, clinical studies showed that different mutations in a single common gene caused all the different severity levels in ADA-SCID cases.<sup>45</sup> Single-gene defects as opposed to multi-gene defects are much easier to isolate and treat.<sup>46</sup> Consequently, treatments for ADA-SCID were developed much earlier than for X-SCID, despite X-SCID being the more prevalent form.<sup>47</sup> Indeed, gene therapy for ADA-SCID was one of the first gene-therapy treatments available and led the way for the gene therapy treatments for X-SCID discussed in this paper.<sup>48</sup> Today, scientists have identified X-SCID as another single gene defect, and have similarly isolated the X-SCID gene.<sup>49</sup>

Despite not understanding all the causes of bubble boy disease, the tragic significance of the disease is exceedingly clear. The children affected with SCID possess immune systems that noticeably lack a distressing amount of essential T cell and B cell functions, which are types of white blood cells and essential to the

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<http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.

<sup>42</sup> “Severe Combined Immunodeficiency,” THE SCID HOMEPAGE at <http://www.scid.net/>.

<sup>43</sup> See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>44</sup> See *id.*

<sup>45</sup> See *id.*

<sup>46</sup> See *id.*

<sup>47</sup> See *id.*

<sup>48</sup> See *id.*

<sup>49</sup> See *id.*



immune system.<sup>50</sup> “This usually results in the onset of one or more serious infections within the first few months of life. These infections are usually serious, and may even be life threatening, they may include pneumonia, meningitis or bloodstream infections.”<sup>51</sup>

When a normal, healthy immune system detects foreign adverse cells, it reacts in different ways to defend the body depending on the type of invasion.<sup>52</sup> One critical way, the way that affects bubble boys, involves white blood cells that identify and destroy invaders.<sup>53</sup> One type of these white blood cells, B cells, make antibodies to mark foreign cells that other cells will attack.<sup>54</sup> Meanwhile, another type of these white blood cells, T cells, make strong chemicals to kill foreign cells.<sup>55</sup> Thus, these B cells and T cells work together to determine which cells are the bad cells, and then to attack and destroy them. Although there are other ways for the immune system to defend the body, the low number and malfunction of T cells in SCID patients is morbid to the body.

Ogden Bruton achieved the first breakthrough in 1952 for the heart-breaking condition of these children, when he discovered that there was an absence of certain proteins, critical to the immune system, in the blood. Through this discovery, Bruton finally found an explanation for immunodeficiency, at least a general, basic explanation. Since then, scientists have now identified over fifty forms of genetically determined

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<sup>50</sup>See “Gene Therapy Cures ‘Bubble Boy,’” NEW SCIENTIST, April 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992124> (“The faulty gene stops the development of T cells, a key part of the immune system.”). See also “Severe Combined Immunodeficiency,” THE SCID HOMEPAGE at <http://www.scid.net/> (“The defining characteristic is usually a severe defect in both the T- & B-lymphocyte systems.”). See also “Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrow.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrow.org/MEDICAL/immune_sys_disorders.html) (“SCID patients either have no B cells and T cells, or those cells have severe defects. Several genetic defects can cause SCID, including not having enough of an enzyme called ADA (adenosine deaminase) and having a defect in the gene that helps shape T cells.”).

<sup>51</sup>“Severe Combined Immunodeficiency,” THE SCID HOMEPAGE at <http://www.scid.net/>.

<sup>52</sup>“Inherited (Congenital) Immune System Disorders,” THE NATIONAL MARROW DONOR PROGRAM at [http://www.marrow.org/MEDICAL/immune\\_sys\\_disorders.html](http://www.marrow.org/MEDICAL/immune_sys_disorders.html).

<sup>53</sup>See *id.* (“White blood cells called lymphocytes identify and destroy invaders.”).

<sup>54</sup>See *id.* (“One type of lymphocyte, a B cell, makes antibodies to mark foreign cells to be attacked.”).

<sup>55</sup>See *id.* (“Another type of lymphocyte, a T cell, makes strong chemicals to kill foreign cells.”).

immunodeficiency diseases, including SCID, which is the most severe of them all. At first, the only way known to guard these children without normal immune systems to protect them, predominantly due to X-SCID, was to make sure they were never exposed to any germs, so they never got any illnesses. “In the past, children with this disorder were kept in strict isolation, sometimes in a plastic tent, leading to the disorder being called ‘bubble boy syndrome.’”<sup>56</sup> This plastic-tent life was hardly ideal, could not completely prevent the children from getting sick, and did not protect the children from being doomed to an early death, but it postponed the inevitable for a brief while.<sup>57</sup>

Then, in 1968, shortly after the discovery of a method to check for matches in transplants,<sup>58</sup> some success with bone marrow transplantation occurred in two patients with otherwise fatal immunodeficiency diseases.<sup>59</sup> This critical discovery played a significant role later in developing treatments for bubble boy disease, whose causes remained unclear at this time. The two patients received transplants of matched<sup>60</sup> bone marrow cells from a matched donor, because bone marrow is a primary source of immune cells. Transplanting bone marrow cells thus offered the patients a new source of immunity. This milestone in SCID research demonstrated that the defect in this immunodeficiency disease was not due to the failure of the marrow to support cell growth, but instead to dysfunction in development of blood cell lines. Unfortunately, early marrow transplants were marked with disappointments. Researchers learned that SCID patients were unusually, and extremely susceptible to graft versus host disease (“GVHD”), a condition caused by the transplanted bone marrow

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<sup>56</sup>“Severe Combined Immunodeficiency Disease,” THE MERCK MANUAL – SECOND HOME EDITION at <http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.

<sup>57</sup>See “Gene Therapy Cures ‘Bubble Boy,’” NEW SCIENTIST, April 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992124> (“Children must be kept in isolation to protect hem from catching infections and usually die young.”).

<sup>58</sup>The discovery of HLA-antigens, certain proteins on cell surfaces that are important in identifying cross matches for transplantation procedures, allowed for researchers to “match” transplant donors and recipients.

<sup>59</sup>“Severe Combined Immunodeficiency Disease,” THE MERCK MANUAL – SECOND HOME EDITION at <http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.

<sup>60</sup>By “matched,” the bone marrow cells had identical HLA-antigens. These “HLA-identical” bone marrow cells allowed transplants to become a reality, instead of just a theory.

T cells reacting against the patient. Hence, on top of the difficulty of finding a matched donor for a bone marrow transplant to become even a possibility, there is the prone danger of SCID children facing an even sooner end by contracting GVHD.

Amidst all these new medical understandings and developments, in 1971, David Vetter was born.<sup>61</sup> David is probably the most famous SCID case.<sup>62</sup> He was the first X-SCID patient given the name “bubble boy,” who lived in isolation in a sterile plastic bubble with filtered air for almost thirteen years, from his birth in 1971 to his death in 1984.<sup>63</sup> From his birth in Texas, David suffered from a genetic mutation leading to SCID.<sup>64</sup> He experienced human touch only once.<sup>65</sup> Sadly, the attempt at treating David with a bone marrow transplant from his older sister failed, because her tissue carried a virus that causes mononucleosis.<sup>66</sup> After the failed operation, David’s likelihood of survival disappeared, and David lived the remaining two weeks of his life outside the bubble, dying before he was even a teenager.<sup>67</sup> “SCID is often called ‘bubble boy disease.’ SCID became widely known during the 1970’s and 80’s, when the world learned of David Vetter, a boy with X-linked SCID, who lived for 12 years in a plastic, germ-free bubble.”<sup>68</sup> It was the later Disney film rendition of David’s life that ensured the notoriety of David, the “bubble boy,” and increased public awareness of bubble boy disease.<sup>69</sup>

Although the cause of immunodeficiency was discovered in 1952, a treatment using bone marrow transplants for immunodeficiency was discovered in 1968, and David made the disease famous from his birth in 1971, the

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<sup>61</sup> See “Severe Combined Immunodeficiency,” THE SCID HOMEPAGE at <http://www.scid.net/>.

<sup>62</sup> See *id.*

<sup>63</sup> See *id.*

<sup>64</sup> See *id.*

<sup>65</sup> See *id.*

<sup>66</sup> See *id.*

<sup>67</sup> See *id.*

<sup>68</sup> *Id.*

<sup>69</sup> See *id.*

disease was nameless until 1975. In 1975, John Soothill, M.D. suggested at the World Health Organization Conference in Geneva that this syndrome should be called severe combined immunodeficiency, and it soon acquired the acronym, SCID. Yet even then, the X-SCID gene remained unidentified, and far from being isolated. Then, in 1990, before the X-SCID gene was identified, the gene therapy treatments for other forms of SCID and for other diseases had already begun.<sup>70</sup>

Thus, gene therapy was never an option for David, because the gene, which when mutated causes X-SCID, the form of SCID that affected David, had not been identified even by 1990, let alone during David's lifetime.<sup>71</sup> Indeed, the biochemical nature of the defect causing X-SCID was not even known.<sup>72</sup> Furthermore, there was no known protein that would have allowed working backward to isolate the gene.<sup>73</sup> As previously mentioned, X-SCID is genetically distinct from ADA-SCID which, at the time, was a better understood form of SCID, and the ADA-SCID gene had been identified and isolated.<sup>74</sup> Even as late as 1990, when gene therapy treatments were available for other diseases,<sup>75</sup> including ADA-SCID, identification of the X-SCID gene seemed unattainable in the near future.<sup>76</sup>

The isolation and cloning of the X-SCID gene occurred sooner than expected, two years later.<sup>77</sup> Then, Japanese researchers in a completely unrelated project published their results in "Science" after finding, isolating, and sequencing the protein that would allow working backward to isolate the X-SCID gene.<sup>78</sup> Just

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<sup>70</sup>See W. French Anderson, "Human Gene Therapy," 392 NATURE 25, 25-30 (1998), also at [http://www.frenchanderson.org/docarticles/pdf/humangenetherapy\\_0498.PDF](http://www.frenchanderson.org/docarticles/pdf/humangenetherapy_0498.PDF).

<sup>71</sup>See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>72</sup>See *id.*

<sup>73</sup>See *id.*

<sup>74</sup>See *id.*

<sup>75</sup>See W. French Anderson, "Human Gene Therapy," 392 NATURE 25, 25-30 (1998), also at [http://www.frenchanderson.org/docarticles/pdf/humangenetherapy\\_0498.PDF](http://www.frenchanderson.org/docarticles/pdf/humangenetherapy_0498.PDF).

<sup>76</sup>See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>77</sup>See *id.*

<sup>78</sup>See *id.*

two years earlier, such a discovery seemed impossible, but this unconnected research hastened the discovery.<sup>79</sup>

In early research, scientists searched for the chromosomal location of the X-SCID gene by studying how the gene segregates families affected with X-SCID.<sup>80</sup> Obviously, the researchers noticed immediately that X-SCID only affected males, and from this observation, deduced that the general chromosomal association was the X chromosome.<sup>81</sup> Any further understanding of the X-SCID gene location on the X chromosome emerged very slowly, because the rarity of X-SCID meant there were very few families available for study of X-SCID carriers.<sup>82</sup> Furthermore, sadly, X-SCID infected boys did not survive long enough for an inclusive research.<sup>83</sup> Finally, comparison of the inheritance pattern of the X-SCID gene with better known X chromosomal functions narrowed its location to a smaller region of DNA, but still one that was too large to isolate, clone, or sequence.<sup>84</sup>

Meanwhile, though, Japanese researchers, in an unrelated project having nothing to do with X-SCID, were studying the structure of a molecule found on the surface of T cells.<sup>85</sup> T cells make and release a small hormone-like molecule which other cells consume to help them respond to an infection.<sup>86</sup> Remarkably and surprisingly, T cells themselves consume the same molecule that they produce.<sup>87</sup> During a response to a particular immune challenge, T cells release this molecule into their immediate vicinity, and then consume some of the molecule they had just released to produce more of their own kind to fight the infection.<sup>88</sup>

The T cell receptor, allowing them to grab this hormone-like molecule, initially was thought to consist of

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<sup>79</sup>See *id.*

<sup>80</sup>See *id.*

<sup>81</sup>See “Gene Therapy Cures ‘Bubble Boy,’” NEW SCIENTIST, April 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992124> (“The disease affects boys because they only have one X chromosome.”).

<sup>82</sup>See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at <http://www.wrclarkbooks.com/downloads/healers.chapter.doc>.

<sup>83</sup>See *id.*

<sup>84</sup>See *id.*

<sup>85</sup>See *id.*

<sup>86</sup>See *id.*

<sup>87</sup>See *id.*

<sup>88</sup>See *id.*

two different protein chains.<sup>89</sup> Yet certain aspects of the receptor's function seemed inconsistent with this two-protein model.<sup>90</sup> The researchers were studying the T cell to explain the disparity in the theory.<sup>91</sup> From their research, they found that there was indeed a third protein chain.<sup>92</sup> The Japanese researchers then isolated and sequenced the protein, and promptly published their discovery.<sup>93</sup>

This description and characterization of the receptor's newly discovered third protein chain explained many of the puzzles relating to the molecule's function.<sup>94</sup> Using this information, a research team at the National Institutes of Health ("NIH") made the connection of this protein with X-SCID.<sup>95</sup> The NIH researchers showed that the protein bound only to the X chromosome, specifically to one location.<sup>96</sup> The NIH researchers further showed that the DNA from every X-SCID patient sampled had mutation in a gene of the third protein.<sup>97</sup> There were no mutations in any of the normal individuals sampled.<sup>98</sup> Thus, it became clear that the gene of the third protein was the gene that, in mutant form, causes X-SCID.<sup>99</sup> "Boys with X-SCID (severe combined immunodeficiency) have a faulty copy of a gene on their X chromosome that makes an immune protein called interleukin-2. As a result, they have no resistance to infection and die unless treated."<sup>100</sup>

From this information, in late 1992, scientists isolated the X-SCID gene, and through the known characteristics of the third protein, understood the exact cause of X-SCID.<sup>101</sup> Children inflicted with X-SCID have the hormone-like molecule to fight off disease, but the malfunctioning third protein prevents them from being able to grab the molecule and properly function. Consequently, the T cells do not perform correctly, and

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<sup>89</sup> See *id.*

<sup>90</sup> See *id.*

<sup>91</sup> See *id.*

<sup>92</sup> See *id.*

<sup>93</sup> See *id.*

<sup>94</sup> See *id.*

<sup>95</sup> See *id.*

<sup>96</sup> See *id.*

<sup>97</sup> See *id.*

<sup>98</sup> See *id.*

<sup>99</sup> See *id.*

<sup>100</sup> See "‘Miracle’ Gene Therapy Trial Halted," NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878>.

<sup>101</sup> See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

X-SCID children are left with virtually no immune protection. However, clinical experiments with a perfect third-protein gene inserted into a retroviral vector showed that this gene can be delivered to bone marrow cells and B cells. These gene therapy treatments promised that there would never be another bubble boy. At this point, the science behind the disease begins to merge with the science behind the treatments, especially gene therapy.

## B. The Treatment

Despite the endless discussions marveling at the breakthrough of gene therapy, the FDA has not approved a single gene therapy for general use.<sup>102</sup> Thus, not one human gene-therapy product is for sale. The possibilities of gene therapy began its promise of miracles for fatally ill patients as early as the 1960s.<sup>103</sup> Yet the FDA refuses to approve gene therapy treatments beyond an experimental phase where individual patients are given a chance at life on a case by case basis. Thus, many people die waiting for their chance at a miracle. Since the halt of the twenty-seven gene therapy trials on January 14, 2003, even fewer patients have a chance at a miracle. Admittedly, while gene therapy may suggest a non-intrusive remedy similar to psychological care, it is an imperfect, dangerous, and precise procedure with multifaceted consequences. Gene therapy techniques can correct defective genes responsible for disease development, but can also mutate healthy genes causing new and different diseases.<sup>104</sup>

For boys affected with bubble boy disease, gene therapy is sometimes the only treatment available. "Treatment with antibiotics and immune globulin is helpful. The best treatment is transplantation of stem cells from bone marrow or umbilical cord blood."<sup>105</sup> However, as discussed above, bone marrow transplants are

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<sup>102</sup>See "Cellular and Gene Therapy," CENTER FOR BIOLOGICS EVALUATION AND RESEARCH at <http://www.fda.gov/cber/gene.htm> ("FDA has not yet approved any human gene therapy product for sale.").

<sup>103</sup>See W. French Anderson, "Human Gene Therapy: The Initial Concepts," GENE THERAPY FOR DISEASES OF THE LUNG, Brigham, K.L., eds.: Marcel Dekker, Inc. (1997) at 3-16, also at [http://www.frenchanderson.org/docarticles/pdf/hgt\\_initial.pdf](http://www.frenchanderson.org/docarticles/pdf/hgt_initial.pdf) ("However,

as early as 1963 Lederberg wrote in an article 'Biological Future of Man': We might anticipate the in vitro culture of germ cells and such manipulations as the interchange of chromosomes and segments. The ultimate application of molecular biology would be the direct control of nucleotide sequences in human chromosomes, coupled with recognition, selection and integration of the desired genes..."). See also "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc) ("The possibilities for applying the emerging techniques of molecular biology to human gene therapy were appreciated by a handful of people as early as the late 1960s.").

<sup>104</sup>These risks particularly emerge in retroviral gene therapy, which uses a type of virus, called a retrovirus, to infect the defective cell and introduce the properly functioning gene. The retroviral can infect many types of cells, besides the defective cell, and can cause serious complications, including death. Thus, retroviral gene therapy, which is used to treat bubble boy disease, entails a much higher risk than other types of gene therapy, and all the gene therapy trials halted by the FDA on January 14, 2003 involved retroviral gene therapy treatments. Retroviruses, the retroviral gene therapy technique, and the risks associated with this technique are discussed in this paper.

<sup>105</sup>"Severe Combined Immunodeficiency Disease," THE MERCK MANUAL - SECOND HOME EDITION at



not always an available or a safe option. Even if transplants and antibiotics were an option for a high percentage, it remains that there are boys without this option. “Gene therapy seems to be effective in some infants who have one form of severe combined immunodeficiency disease. Gene therapy consists of removing some white blood cells from the infant, inserting a normal gene into the cells, and returning the cells to the infant.”<sup>106</sup>

There are many gene therapy approaches, using different methods to introduce healthy genes into the body, each with different types of risks. In the most common gene-therapy procedure, researchers insert a normal gene into the body to replace a nonfunctional gene. A second distinct method swaps an abnormal gene for a normal gene. A third method repairs the abnormal gene through reverse-mutation to returns the gene to its normal function. A fourth method alters the strength of the abnormal gene to prevent it from functioning at all.

The idea is simple but the actualization is much more complicated. These methods require using viruses to invade the body, but with healthy genes instead of sickly genes. These viruses serve as viral vectors in the gene therapy treatment to direct the healthy genes to different locations in the body. The danger of using viral vectors is that they create additional complications, including the risk of viral infection. However, non-viral vectors, as an alternative to viral vectors, while presenting fewer complications, are thus far much less efficient at introducing the healthy genes into the body.

There are four classes of viruses used in gene therapy treatments. One class of viruses, adenoviruses, have double-stranded DNA genomes that typically cause respiratory, intestinal, and eye infections in humans, like the virus that causes the common cold. Adenoviral vectors target a wide range of cells, allowing for a high probability of effectiveness. Yet adenoviral vectors are non-integrating, which means they do not incorporate

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<sup>106</sup><http://www.merck.com/mrkshared/mmanual.home2/sec16/ch184/ch184i.jsp>.  
*Id.*

themselves into the body permanently, and must be reintroduced repeatedly to treat gene therapy patients. Another class of virus used in gene therapy treatments, adeno-associated viruses, are small, single-stranded DNA viruses that can insert their genetic material only at one fixed chromosomal location, making them nonrealistic options for many gene therapy patients. A third class of viruses, herpes-simplex viruses, like the virus that causes cold sores, are double-stranded DNA viruses that also can only infect a particular cell type, neurons, similarly making them less valuable in gene therapy treatments. Unfortunately, none of these classes of viruses can be used to treat bubble boy disease.

The class of viruses used in treating bubble boy disease is retroviruses, which create double-stranded DNA copies of their genomes that can be integrated into the chromosomes of host cells very effectively. A familiar retrovirus, namely the human immunodeficiency virus (“HIV”), more commonly referred to by its acronym, reveals the menacing characteristics of this virus.<sup>107</sup> The quality that allows HIV to incorporate itself quickly in the body, threatening fatal and permanent damage to the immune system, makes retroviral vectors very good at integrating with the body to deliver healthy genes for long-term, ideally permanent, remedies. Yet retroviruses, like adenoviruses, can integrate into a wide range of cells, increasing their utility in gene therapy treatments, but also increasing the risk of infecting the wrong cell, since they randomly integrate, sometimes in regions where they should not. “Gene therapy involved shuttling the gene into a patient’s cells using a harmless virus. But transferred genes cannot be targeted to insert into a specific part of the chromosome.”<sup>108</sup> This characteristic explains the reason the gene therapy treatment that cured the two children may have integrated into the gene that causes leukemia. Furthermore, retroviruses, unlike adenoviruses, can integrate permanently, promising a permanent cure while threatening permanent damage. Finally, retroviruses only infect rapidly dividing cells, which increases the chance that the treatment will have quick results. However,

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<sup>107</sup>See W. French Anderson, “Human Gene Therapy,” 392 NATURE 25, 25-30 (1998), also at [http://www.frenchanderson.org/docarticles/pdf/humangenetherapy\\_0498.PDF](http://www.frenchanderson.org/docarticles/pdf/humangenetherapy_0498.PDF).

<sup>108</sup>See “‘Miracle’ Gene Therapy Trial Halted,” NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878>.

this characteristic also specifically increases the risk of leukemia, a disease where blood cells proliferate out of control, since the gene that causes leukemia is a rapidly dividing gene.

Scientists began isolating and sequencing proteins since the 1950s. With the complete amino acid sequence of a protein and using the genetic code, it is possible to work backwards and predict the sequence of the corresponding gene.<sup>109</sup> However, individual genes could not yet be isolated, and thus gene therapy remained only a theoretical possibility. Yet the dream of gene therapy grew with the breakthrough of the 1960s, when physician and scientist Stanfield Rogers observed that viruses could deliver genes, one of the founding blocks to modern gene therapy.<sup>110</sup> Rogers was using rabbits to study one of the genes carried by a common wart-causing virus.<sup>111</sup> This gene encodes a certain enzyme that degrades excess amount of an amino acid, a building block of protein, as discussed above.<sup>112</sup> In rabbits infected with this virus, the levels of this amino acid in the blood were unusually low.<sup>113</sup> Then, upon removing blood samples from people in the laboratory, Rogers found that laboratory personnel handling the infected rabbits had become infected with the virus, not an uncommon occurrence in the laboratory.<sup>114</sup> The critical finding, however, was that these people also had extremely low levels of this amino acid.<sup>115</sup> This finding proved that genes carried as part of a viral genome could alter normal physiological processes in a human being.<sup>116</sup> Thus, viruses could theoretically deliver genes to different cells in the human body.<sup>117</sup> Of course, at this point, human genes had never been isolated, and thus gene therapy remained only an idea, but the possibilities for applying the emerging techniques of molecular biology to human gene therapy were born. Subsequently, in 1967, Marshall Nirenberg, the Nobel

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<sup>109</sup>See Peter B. Hutt and Richard A. Merrill, "Regulation of Biotechnology," FOOD AND DRUG LAW: CASES AND MATERIALS, Westbury, NY: The Foundation Press Inc (1991) at 964-985 (noting that the James Watson and Francis Crick discovery of 1953, the double-helix structure of DNA, opened the field of molecular biology and led to the possibility of gene therapy).

<sup>110</sup>See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>111</sup>See *id.*

<sup>112</sup>See *id.*

<sup>113</sup>See *id.*

<sup>114</sup>See *id.*

<sup>115</sup>See *id.*

<sup>116</sup>See *id.*

<sup>117</sup>See *id.*

Prize winner, wrote of programming cells with synthetic messages, making the subject of gene therapy into an ethical debate.<sup>118</sup>

In the 1970s, isolating individual genes became a possibility.<sup>119</sup> Thus, the theoretical advances discussed above, from knowing the complete amino acid sequences of quite a few proteins, came together and made isolating genes a reality.<sup>120</sup> In 1977, the first human gene, part of the oxygen-carrying molecule of red blood cells, was isolated and cloned.<sup>121</sup> Defects in this gene can cause diseases like severe anemia,<sup>122</sup> which is the inability to make red blood cells and is life-threatening.<sup>123</sup> Subsequently, a physician at UCLA, Dr. Martin Cline, working with another UCLA scientist, tried introducing the gene into mouse bone marrow cells using a viral vector.<sup>124</sup> The experiment worked.<sup>125</sup> More importantly, when the altered bone marrow cells were put back into mice, there was evidence that they survived and that the added gene was functioning.<sup>126</sup> The researchers then applied to their university's Human Subjects Protection Committee, an institutional review board ("IRB"), for permission to try the same thing in human patients with severe anemia.<sup>127</sup> Unable to get permission from UCLA, Cline recruited patients suffering from this condition in foreign institutions.<sup>128</sup>

Several patients had samples of their bone marrow removed, exposed to the vector containing the healthy

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<sup>118</sup>See John C. Fletcher, "Evolution of Ethical Debate About Gene Therapy," 1 HUMAN GENET THERAPY 55, 55-60 (Spring 1990) (tracing the development of gene therapy from the beginnings by Nobelist Marshall Nirenberg).

<sup>119</sup>See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>120</sup>See *id*

<sup>121</sup>See LeRoy Walters, "Ethical Issues in Human Gene Therapy," 2 JOURNAL OF CLINICAL ETHICS 267, 267-274 (Winter 1991) (discussing the unauthorized experiment of Martin Cline after hemoglobin, the gene in red blood cells responsible for carrying oxygen to the entire body was isolated).

<sup>122</sup>This disease discussed here is thalassemia, which is a genetic blood disorder when the body can not make enough hemoglobin, a part of the red blood cells that carries oxygen to all of the body. Thalassemia is one of the most serious forms of anemia, which is the more general disorder describing an absence of functioning red blood cells.

<sup>123</sup>See LeRoy Walters, "Ethical Issues in Human Gene Therapy," 2 JOURNAL OF CLINICAL ETHICS 267, 267-274 (Winter 1991) (discussing the unauthorized experiment of Martin Cline).

<sup>124</sup>See *id*

<sup>125</sup>See *id*

<sup>126</sup>See *id*.

<sup>127</sup>See *id*.

<sup>128</sup>See *id*.

gene, and then infused back into their bloodstream.<sup>129</sup> The experiment failed to alter the course of their disease, but the patients appeared to suffer no harm from the procedure either.<sup>130</sup> His institution, the federal government, and the international scientific community denounced Martin severely.<sup>131</sup> Thus, the first attempt at gene therapy using cloned DNA destroyed hopes with the poor results and the negative response from the community. Nonetheless, the research continued.

In 1983, three separate laboratories published the gene sequence encoding ADA, one of the earlier human genes to be isolated and cloned for study, and the malfunction of which causes ADA-SCID.<sup>132</sup> In the late summer of 1990, the NIH Recombinant DNA Research Advisory Committee (“RAC”), working with the FDA, and the FDA finally were sufficiently convinced by the preliminary laboratory data to approve the first human gene therapy trial.<sup>133</sup> Thus, in 1990, National Institutes of Health (“NIH”) doctors conducted the first clinical trial of gene therapy.<sup>134</sup> It succeeded.<sup>135</sup> A four-year-old girl named Ashanti DeSilva received genetically altered cells to fix a rare condition she had inherited at birth.<sup>136</sup> That rare condition happened to be a form of SCID, although ADA-SCID, not X-SCID.<sup>137</sup> DeSilva had been in advanced stages of her disease, and standard therapies were not working.<sup>138</sup>

Before final FDA approval had been obtained for the entire gene therapy procedure, samples of T cells were collected from DeSilva’s blood and infected with the ADA vector in vitro.<sup>139</sup> The cells were first triggered to start dividing, in order to enhance penetration by the retroviral vector.<sup>140</sup> After exposure to the virus, the

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<sup>129</sup> See *id.*

<sup>130</sup> See *id.*

<sup>131</sup> See *id.*

<sup>132</sup> See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>133</sup> See *id.*

<sup>134</sup> See *id.*

<sup>135</sup> See *id.*

<sup>136</sup> See *id.*

<sup>137</sup> See *id.*

<sup>138</sup> See *id.*

<sup>139</sup> See *id.*

<sup>140</sup> See *id.*

cells were grown in an incubator for about a week to expand their total numbers.<sup>141</sup> Final FDA approval was received on the morning of September 14, 1990.<sup>142</sup> In that afternoon, four-year-old DeSilva was infused with her own T cells containing the retroviral ADA vector, and became the first human being in history to undergo gene therapy for therapeutic purposes.<sup>143</sup>

The procedure went smoothly.<sup>144</sup> Her white blood cells received a gene that makes an immune system protein, the third protein of a T cell, that she lacked.<sup>145</sup> The genetically treated white blood cells perform for only a few months, because the T cells do not live very long unless stimulated from fighting off foreign cells.<sup>146</sup> Thus, the effect is only transient, because the gene therapy treatment for ADA-SCID transforms the T cells.<sup>147</sup> However, stimulated T cells become long-lived “memory” T cells, and these previously generated memory cells normally handle most of an immune response.<sup>148</sup> Over time, a SCID patient in whom even a small proportion of T cells were kept alive long enough to be stimulated might build up a repertoire of T cells capable of responding to most types of foreign cells.<sup>149</sup> This situation describes the prognosis for DeSilva.<sup>150</sup> For a while, she had to continue to receive gene therapy on a regular basis.<sup>151</sup> After four infusions over a four-month period, DeSilva’s T cell counts were climbing toward normal. Direct analysis of DeSilva’s T cells showed that nearly all of them expressed the newly inserted ADA gene.<sup>152</sup> Today, DeSilva is relatively healthy, lives a normal life, and no longer receives gene therapy treatments of infusions of gene-altered T cells.<sup>153</sup> DeSilva’s daily existence illustrates the hope of gene therapy attained, and explains the ceaseless

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<sup>141</sup> See *id.*

<sup>142</sup> See *id.*

<sup>143</sup> See *id.*

<sup>144</sup> See *id.*

<sup>145</sup> See *id.*

<sup>146</sup> See *id.*

<sup>147</sup> See *id.*

<sup>148</sup> See *id.*

<sup>149</sup> See *id.*

<sup>150</sup> See *id.*

<sup>151</sup> See *id.*

<sup>152</sup> See *id.*

<sup>153</sup> DeSilva is now 17 years old and is considered a success story for gene therapy. See “Gene Therapy Turns 10,” CURRENT SCIENCE, January 19, 2001 at [http://www.findarticles.com/cf\\_dls/m0BFU/10.86/69527187/p1/article.jhtml](http://www.findarticles.com/cf_dls/m0BFU/10.86/69527187/p1/article.jhtml).

hope for those, like “bubble boys,” to try this treatment as well.

One of the conditions imposed by the Recombinant DNA Research Advisory Committee (“RAC”) was that DeSilva and subsequent patients receiving ADA-SCID gene therapy continue taking PEG-ADA.<sup>154</sup> PEG-ADA is a drug, ADA protein, which had been approved by the FDA as a standard treatment for ADA-SCID in 1990, just shortly before the Recombinant DNA Research Advisory Committee (“RAC”) approved ADA gene therapy.<sup>155</sup> In many children, PEG-ADA causes a marked initial increase in the number of T cells, alleviating many of the complications of ADA-SCID.<sup>156</sup> On the other hand, some children gain little or no sustainable benefit after a few administrations of the ADA drug, and it is enormously expensive, more than two hundred thousand dollars per year for the average patient.<sup>157</sup> PEG-ADA does not correct the underlying defect, but simply alleviates its symptoms, and thus must be taken regularly for the life of the patient.<sup>158</sup> DeSilva was being treated with PEG-ADA at the time she began gene therapy. Although she did not seem to be responding to the drug, it was considered inappropriate to discontinue its use.<sup>159</sup> Hence, evaluation of gene therapy in its first and longest lasting trial is complicated by the continued administration of a drug with the same potential effect of gene therapy, an increase in viable T cells.<sup>160</sup>

Some investigators feel that the PEG-ADA may actually be working against the effectiveness of the underlying gene therapy treatment.<sup>161</sup> PEG-ADA helps keep all T cells alive, whether or not they are malfunctioning.<sup>162</sup> From a gene therapist’s point of view, PEG-ADA is helping “bad” as well as “good” T cells

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<sup>154</sup>See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at <http://www.wrclarkbooks.com/downloads/healers-chapter.doc>.

<sup>155</sup>See *id.*

<sup>156</sup>See *id.*

<sup>157</sup>See *id.*

<sup>158</sup>See *id.*

<sup>159</sup>See *id.*

<sup>160</sup>See *id.*

<sup>161</sup>See *id.*

<sup>162</sup>See *id.*

to survive.<sup>163</sup> There is reason to believe that, in the absence of PEG-ADA, those T cells infected with a healthy ADA gene would have a selective advantage for survival, and would eventually outgrow and displace the malfunctioning T cells.<sup>164</sup> However, they were unable to convince the RAC and FDA to allow them to wean DeSilva or other patients off the PEG-ADA in order to find out.<sup>165</sup>

In September 1999, gene therapy suffered a major setback with the first death from gene therapy, eighteen-year-old Jesse Gelsinger, an otherwise relatively healthy patient.<sup>166</sup> Gelsinger was participating in a gene therapy trial for a metabolic disorder.<sup>167</sup> A severe negative immune response to the high dose of an early-generation adenoviral vector caused multiple organ failures, including failure of the liver, kidney, and lungs. Four days after starting the treatment, Gelsinger passed away. Following Gelsinger's death, government officials investigated the treatment and found that gene therapy researchers were careless with patient safety, and were even neglecting to report deaths.<sup>168</sup> Gelsinger's death resulted in decreased clinical participation, tighter regulations, and more obstacles for researchers.<sup>169</sup> Nonetheless, gene therapy persevered, albeit a bit more slowly.<sup>170</sup>

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<sup>163</sup> See *id.*

<sup>164</sup> See *id.*

<sup>165</sup> See *id.*

<sup>166</sup> See Sally Lehrman, "Virus Treatment Questioned After Gene Therapy Death," 401 NATURE 517, 517-18 (October 7, 2001) and at <http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v401/n6753/full/401517b0.fs.html> (discussing the setback of gene therapy after Gelsinger's death).

<sup>167</sup> See Joan Stephenson, "Studies Illuminate Cause of Fatal Reaction in Gene-Therapy Trial," 285 JAMA: THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 2570 (May 23-30, 2001) and at <http://jama.ama-assn.org/cgi/content/full/285/20/2570> (discussing the cause of Gelsinger's death eight months later).

<sup>168</sup> See United States Congress, Senate, Committee on Health, Education, Labor and Pensions, Subcommittee on Public Health, "Gene Therapy: Is There Oversight for Patient Safety?: Public Hearing," Washington, D.C.: Unpublished testimonies and documents from the hearing, 69 pages (February 2, 2000) (featuring testimony from Gelsinger's father, gene therapy patients, and medical experts).

<sup>169</sup> *Id.* See also Alfred J. Smuskiewicz, "Genetic Medicine Update," WORLD BOOK, 2001 at <http://home.earthlink.net/~ajjsart/genmedwb.html> ("Gelsinger's death triggered action by federal health authorities to strengthen monitoring and regulation of gene therapy experiments in the United States. In March 2000, the FDA and the U.S. National Institutes of Health (NIH) announced that they planned to conduct more unscheduled inspections of gene therapy facilities and maintain greater oversight of gene therapy experiments. The agencies also said they would provide more information to scientists and the public.").

<sup>170</sup> See Trisha Gura, "After a Setback, Gene Therapy Progresses... Gingerly," 291 SCIENCE 1692, 1692-1697 (March 2, 2001) and at <http://www.sciencemag.org/cgi/content/full/291/5509/1692> (discussing the slow progression of gene therapy treatment for hemophilia in light of Gelsinger's death).



### III. THE REGULATOR

#### A. The FDA and the NIH

The curt story of the science behind bubble boy disease is depressing at best. Bubble boy disease destroys the immune system, insuring a very early death if left untreated. The available treatments are limited mostly to bone marrow transplants, which require a matched donor and come with the high risk of graft versus host disease (“GVHD”), which is also fatal. Gene therapy trials were extremely promising, curing every boy treated, but alas had different risks. Furthermore, the FDA has since halted all the trials after two of the fifteen boys treated developed leukemia-like symptoms.

Thus, the dismal future of the bubble boys reduces to the connected and much more complicated story of the FDA, whose far-reaching, well established, and strong authoritative role began with a congressional mandate. The FDA, a part of the Department of Health and Human Services since 1979, obtains its authority under the Federal Food, Drug, and Cosmetic Act of 1938.<sup>171</sup> “Authorized by Congress to enforce the Federal Food, Drug, and Cosmetic Act and several other public health laws, the agency monitors the manufacture, import, transport, storage, and sale of \$1 trillion worth of goods annually, at a cost to taxpayers of about \$3 a person.”<sup>172</sup> Congress, however, could not have known the questions the FDA faces today. The FDA’s objectives, guidelines, and procedures determine the decisions that allow some treatments but not others, including those decisions that affect babies fighting for their lives against bubble boy disease.

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<sup>171</sup> See Peter B. Hutt and Richard A. Merrill, “The Federal Food, Drug, and Cosmetic Act of 1938,” *FOOD AND DRUG LAW: CASES AND MATERIALS*, Westbury, NY: The Foundation Press Inc (1991) at 6. See also “Frequently Asked Questions,” U.S. FOOD AND DRUG ADMINISTRATION at <http://www.fda.gov/opacom/faqs/faqs.html> (noting the 1979 amendment to the 1938 Act in 93 Stat. 668, 695 (1979)).

<sup>172</sup> See “Designation and Locations of FDA in Federal Government,” U.S. FOOD AND DRUG ADMINISTRATION at <http://www.fda.gov/opacom/morechoices/designat.html>.

In 1974, the National Institutes of Health (“NIH”) began regulating recombinant DNA research.<sup>173</sup> The Recombinant DNA Research Advisory Committee (“RAC”) to the NIH Director was also created at this time.<sup>174</sup> The RAC approves all research projects involving recombinant DNA in laboratories in the United States, handles gene-marking research, and reviews all gene therapy trials with the FDA.<sup>175</sup> In other words, the RAC oversees all federally funded research involving recombinant DNA.<sup>176</sup> The intrusion of the RAC into clinical trials involving recombinant DNA grew out of a defining moment in the history of molecular biology.<sup>177</sup>

Scientists began making recombinant DNA molecules almost as soon as it became possible in the 1970s. The initial experiments figured out only *the conditions* necessary for cutting and stitching together pieces of DNA from various sources in test tubes. Before long, scientists were eager to move on to more interesting and practical possibilities. Thus, some scientists began carrying out experiments involving intact genomes removed from bacteria and viruses.

In 1973, Herb Boyer and Stanley Cohen created the first biologically functional recombinant DNA molecule. They had placed a toad gene into bacteria. The bacteria promptly began making the corresponding toad protein. Scientists closely followed the new, widely known experiments with recombinant DNA, and started to get nervous. No one had ever before tampered with the genome of a living organism. There was no evidence that such experiments were in fact dangerous, but the suggestion was made that all the scientists involved should suspend further experimentation until the community had a discussion.

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<sup>173</sup>See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>174</sup>See *id.*

<sup>175</sup>See *id.*

<sup>176</sup>See *id.*

<sup>177</sup>See *id.*

The meeting to discuss the implications and possible risks of recombining the DNA of living organisms took place at the Asilomar Conference Center near Monterey, California, in 1974.<sup>178</sup> All of the major laboratories working with recombinant DNA attended, along with representatives of the federal agencies funding this research.<sup>179</sup> Out of this meeting came a proposal to ask the prestigious National Academy of Sciences to establish a committee to review the current status of recombinant DNA technology.<sup>180</sup> This committee would also advise the government whether and how to regulate such research using this technology. The committee ultimately recommended that the NIH permanently establish the RAC, which the NIH formed almost immediately.<sup>181</sup> Over the next two years, the RAC began formulating guidelines for carrying out recombinant DNA research funded by federal research grants.<sup>182</sup> NIH published these guidelines in 1976.<sup>183</sup> Almost immediately, virtually all laboratories in the United States carrying out such research, however funded, adopted the guidelines.<sup>184</sup> Indeed, most governments throughout the world also eventually adopted the guidelines in one form or another.<sup>185</sup>

The early workings of the RAC dealt almost exclusively with safety issues for laboratory research.<sup>186</sup> The major concern initially was that altered life forms would escape from laboratories and infect plants, animals, or people on the outside.<sup>187</sup> RAC, in responding to this concern, disseminated guidelines for “containment” procedures, handling and storage of recombinant DNA, and other practical issues, to research laboratories throughout the country.<sup>188</sup> Institutions sponsoring such research were required to establish institutional

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<sup>178</sup> *See id.*

<sup>179</sup> *See id.*

<sup>180</sup> *See id.*

<sup>181</sup> *See id.*

<sup>182</sup> *See id.*

<sup>183</sup> *See id.*

<sup>184</sup> *See id.*

<sup>185</sup> *See id.*

<sup>186</sup> *See id.*

<sup>187</sup> *See id.*

<sup>188</sup> *See id.*

review boards (“IRB”) to ensure implementation of the RAC guidelines, and to assure that all applications for government research funding submitted to NIH met RAC standards.<sup>189</sup> Mindful of the furor that had attended the earlier forays in the direction of human gene therapy, the RAC also established a permanent Human Gene Therapy Subcommittee.<sup>190</sup> This subcommittee took on the task of carrying out initial reviews of all research involving human genes, whether intended for therapeutic purposes or not.<sup>191</sup> The government later decided that any proposals to introduce DNA into human beings would also be subject to clinical trials as defined by the FDA.<sup>192</sup> Thus, for the time being, both the RAC and the FDA approved clinical trials for gene therapy.<sup>193</sup> When gene therapy moved out of the laboratory and into humans, there was a move on the part of some biotechnology companies and a few academics to have the RAC abolished, and to transfer sole authority for approving clinical trials to the FDA.<sup>194</sup> However, the unique role the RAC plays in assessing the quality and value of the basic science underlying and likely to emerge from clinical trials was a considerable value.<sup>195</sup>

In 1996, the review of individual gene-therapy protocols became the sole responsibility of the FDA. However, the RAC continues to review protocols that involve new technologies, and to recommend regulatory changes based on evolving techniques. The FDA oversees the safety and efficacy of the genetically altered products, the safety of the manufacturing process, and control of the final product. Within the FDA, the Center for Biologics Evaluation and Research (“CBER”) regulates gene therapy. “CBER is the Center within the FDA responsible for ensuring the safety and efficacy of blood and blood products, vaccines, allergenics, and biological therapeutics. CBER’s regulation of biological products has expanded in recent years to include a wide variety of new products such as biotechnology products, somatic cell therapy and gene therapy, and

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<sup>189</sup> *See id.*

<sup>190</sup> *See id.*

<sup>191</sup> *See id.*

<sup>192</sup> *See id.*

<sup>193</sup> *See id.*

<sup>194</sup> *See id.*

<sup>195</sup> *See id.*

banked human tissues.”<sup>196</sup> Gene therapy, as a biologic, is subject to the regulations under the Public Service Health Act, as well as the Federal Food, Drug, and Cosmetic Act. “Biologics have been predominantly regulated under the Public Health Service Act although they are also defined as drugs under the Food Drug and Cosmetic Act.”<sup>197</sup> Gene therapy thus endures an extraordinarily difficult review process. “Gene transfer clinical trials have a unique oversight process administered by the National Institutes of Health (NIH), through the Recombinant DNA Advisory Committee (RAC) and the NIH Guidelines for Research Involving Recombinant DNA molecules, and the Food and Drug Administration (FDA) through review and approval of gene therapy protocols and premarket approval requirements for gene therapy products.”<sup>198</sup>

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<sup>196</sup> See “Frequently Asked Questions,” CENTER FOR BIOLOGICS EVALUATION AND RESEARCH at <http://www.fda.gov/cber/faq.htm>.

<sup>197</sup> See *id.*

<sup>198</sup> See “Gene Transfer,” GENETICS AND PUBLIC POLICY CENTER at [http://www.dnapolicy.org/genetics/transfer.jhtml;\\$sessionid\\$4I4DCIQAACY4](http://www.dnapolicy.org/genetics/transfer.jhtml;$sessionid$4I4DCIQAACY4)

## B. The Trials

Before the FDA became involved a few decades ago in 1962, clinical trials were generally informally organized studies carried out by physicians, usually in collaboration with drug companies, to test a new drug, medical device or clinical procedure.<sup>199</sup> These studies were often not standardized, lacked important controls, and did not pay attention to proper statistical analysis of data.<sup>200</sup> Consequently, many clinical trials produced data of little real value.<sup>201</sup> Yet patients were put at risk during such trials, and patients subsequently treated by drugs or devices approved for general use as a result of faulty clinical trials were unknowingly also at risk.<sup>202</sup>

Starting in the 1970s, the federal government began formulating specific sets of guidelines for clinical trials.<sup>203</sup> Today, all new drugs and invasive medical devices are subject to rigorously controlled clinical tests before being available for general clinical use.<sup>204</sup> Clinical trials in the United States are overseen by the FDA, and the FDA has final authority for approving a new drug or invasive medical device for manufacture, marketing, and general use by the medical community at large.<sup>205</sup> Clinical trials are most often carried out in university medical centers under the guidance of physicians who also have strong basic science backgrounds, or have basic science consultants as part of the overall clinical trial team.<sup>206</sup> In most cases, a potential manufacturer or marketer of a new drug or procedure will be an active partner in clinical trials, providing the drug itself and any other materials needed for the trials, and generally underwriting their costs.<sup>207</sup>

As discussed above, one of the major RAC guidelines is that all institutions sponsoring clinical trials must

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<sup>199</sup> See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>200</sup> See *id.*

<sup>201</sup> See *id.*

<sup>202</sup> See *id.*

<sup>203</sup> See *id.*

<sup>204</sup> See *id.*

<sup>205</sup> See *id.*

<sup>206</sup> See *id.*

<sup>207</sup> See *id.*

have an internal institutional review board (“IRB”) to review clinical trial proposals before they are even submitted for FDA approval.<sup>208</sup> The IRB, sometimes called the Human Subjects Protection Committee, carries out an initial assessment of the scientific soundness of the proposal, and makes certain that the data collection and analysis procedures are valid and meaningful.<sup>209</sup> Furthermore, the IRB determines that the proposed patient population is appropriate for the aims of the trial, and that the proposal follows the proper patient informed consent procedures.<sup>210</sup> Similarly, all gene therapy treatments fall under these same clinical procedures.<sup>211</sup>

Before a clinical trial can begin, the FDA must see compelling evidence from laboratory studies that a proposed new drug or procedure is safe in animal and in vitro studies.<sup>212</sup> This preclinical phase of testing generally involves laboratory experiments with human cells grown outside the body, to gain insight into potential toxicity and to be sure that the drug will be safe for humans.<sup>213</sup> The next step is to test the drug or procedure in animals.<sup>214</sup> This work often begins with rats and mice, for reasons of economy and because of the large backlog of experience with these animals and knowledge of how their physiology compares with humans.<sup>215</sup> A very useful animal model that finds increasing use in drug testing is the so-called nude mouse.<sup>216</sup> Nude mice have a genetic defect that prevents them from immunologically rejecting human cells and tissues.<sup>217</sup> A closely linked defect prevents them from developing fur, hence the “nude” designation.<sup>218</sup> It is thus possible to transplant into nude mice a small piece of the human tissue a new drug is supposed to affect, to inject that drug into the mice, and to monitor the drug’s effect on the human tissue.<sup>219</sup> In

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<sup>208</sup> See *id.*

<sup>209</sup> See *id.*

<sup>210</sup> See *id.*

<sup>211</sup> See *id.*

<sup>212</sup> See *id.*

<sup>213</sup> See *id.*

<sup>214</sup> See *id.*

<sup>215</sup> See *id.*

<sup>216</sup> See *id.*

<sup>217</sup> See *id.*

<sup>218</sup> See *id.*

<sup>219</sup> See *id.*

some cases, it may be appropriate to test the drug further on a larger animal before testing in humans, but increasingly the nude mouse model has been able to satisfy federal regulators.<sup>220</sup>

Ultimately, of course, any new drug or procedure must be tested on human beings to be absolutely certain it is safe and has the effect intended by its developers.<sup>221</sup> The FDA has developed very strict guidelines for conducting human clinical trials.<sup>222</sup> The first principle of any clinical trial is fully informed consent of the human subjects who will participate in the trial.<sup>223</sup> Patients must clearly understand the experimental nature of the procedures they will undergo, the possible dangers they may face, and the uses of the gathered information.<sup>224</sup> Researchers cannot mislead patients about benefits to their underlying disease, or risks of the treatment.<sup>225</sup> Researchers must assure confidentiality of the patient information.<sup>226</sup> The FDA must review a copy of information provided to each patient as part of the overall approval process for any new clinical trial.<sup>227</sup>

Most clinical trials proceed in four phases.<sup>228</sup> The FDA reviews each phase while it proceeds, and each phase must be completed and approved before the next phase can begin.<sup>229</sup> Although the exact description of each phase may be slightly different for each new drug or procedure, the following general guidelines apply to the majority of trials conducted.<sup>230</sup> In the first phase, investigators look at how long the drug remains in the system.<sup>231</sup> The FDA observes whether its properties change once it is inside a human body, and whether it causes any measurable side effects, either as reported by the subject or as detected in laboratory tests.<sup>232</sup>

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<sup>220</sup> See *id.*

<sup>221</sup> See *id.*

<sup>222</sup> See *id.*

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<sup>225</sup> See *id.*

<sup>226</sup> See *id.*

<sup>227</sup> See *id.*

<sup>228</sup> See *id.*

<sup>229</sup> See *id.*

<sup>230</sup> See *id.*

<sup>231</sup> See *id.*

<sup>232</sup> See *id.*



The first phase usually tests a range of dosages that are guided by earlier toxicity tests on animals.<sup>233</sup> Sometimes the first phase tests infected persons, and sometimes the first phase tests healthy volunteers.<sup>234</sup> When first phase tests the drug on infected persons, the patients are usually battling advanced stages of the disease and have failed to respond to standard current therapies for the disease.<sup>235</sup> The number of patients involved in this first phase is particularly few, no more than the number required to get preliminary data for the points under study.<sup>236</sup> Thus, at this phase, typically less than ten individuals have a chance to receive the treatment.<sup>237</sup>

During the second phase, investigators focus on the effectiveness of the new treatment.<sup>238</sup> Dosage and toxicity limits derived from the first phase are used to design the larger-scale second phase trials to begin assessing the value of the new drug or treatment as compared to existing treatments.<sup>239</sup> The second phase may test patients with less advanced stages of disease.<sup>240</sup> Investigators continue to monitor patients closely for toxicity and any side effects.<sup>241</sup> In this second phase, a larger numbers of patients are usually involved, up to a few hundred individuals.<sup>242</sup>

At the third phase, larger numbers of patients, up to thousands of individuals, are tested in a variety of clinical settings, including community hospitals, university medical centers, and private facilities.<sup>243</sup> Additional data on the interaction of the new drug with existing drugs used to treat the disease are gathered.<sup>244</sup> Information gathered in the third phase will eventually be used to instruct physicians about use of the new drug.<sup>245</sup>

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<sup>233</sup> See *id.*

<sup>234</sup> See *id.*

<sup>235</sup> See *id.*

<sup>236</sup> See *id.*

<sup>237</sup> See *id.*

<sup>238</sup> See *id.*

<sup>239</sup> See *id.*

<sup>240</sup> See *id.*

<sup>241</sup> See *id.*

<sup>242</sup> See *id.*

<sup>243</sup> See *id.*

<sup>244</sup> See *id.*

<sup>245</sup> See *id.*

Toxicity is still closely monitored.<sup>246</sup> The drug developer will usually apply for formal approval from the FDA to market the new drug after successful conclusion of the third phase of clinical trials.<sup>247</sup>

The fourth and final phase of clinical trials occurs after the drug is approved by the FDA, and is required to continue studying the effects of the drug after general release.<sup>248</sup> In this fourth phase, the drug may be extended to slightly different patient populations than those studied in earlier trials, or dosages may be altered, or the drug tested in combinations with other previously-approved drugs.<sup>249</sup> The drug may also be extended for use in related conditions not specified in the original trials.<sup>250</sup>

Clinical trials test new products before allowing them to be sold publicly.<sup>251</sup> Thus, these strict and time-consuming phases are often very important to produce sound, scientifically meaningful information about proposed new drugs, devices, or procedures, and protect the patients involved in the trials.<sup>252</sup> They represent the transition phase between highly promising basic laboratory research on a new drug or treatment method, and the general release of that drug or treatment to the larger medical community for use in standard therapy.<sup>253</sup> Thus, clinical trials represent a riskier choice rather than waiting for FDA approval.<sup>254</sup>

However, others view these phases as overly rigid and risk-averse, especially in dealing with life-threatening diseases and patients who have no hope to still be alive when the treatments are finally approved. For instance, scores after discovering the promise of gene therapy,<sup>255</sup> decades after perfecting the science,<sup>256</sup> and years after testing on nude mice,<sup>257</sup> human gene therapy was finally ready *just* to begin the clinical trial

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<sup>246</sup> See *id.*

<sup>247</sup> See *id.*

<sup>248</sup> See *id.*

<sup>249</sup> See *id.*

<sup>250</sup> See *id.*

<sup>251</sup> See *id.*

<sup>252</sup> See *id.*

<sup>253</sup> See *id.*

<sup>254</sup> See *id.*

<sup>255</sup> See “Gene Therapy: The First Halting Steps,” THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc) (“The possibilities for applying the emerging techniques of molecular biology to human gene therapy were appreciated by a handful of people as early as the late 1960s.”).

<sup>256</sup> See *id.* (“By 1987 Anderson had prepared an initial proposal for clinical trials using the cloned human ADA gene to treat patients with ADA-SCID.”).

<sup>257</sup> Indeed, there were expectations that clinical trials for gene therapy of X-SCID would be underway in the

process. However, by this time, fifty years later, many bubble boys had died. Furthermore, gene therapy introduced some new complications and concerns that scared the FDA into making the approval process even more difficult than it had been in the past. Thus, clinical trials often represent the only chance at a cure, when waiting means certain death.

It was this later situation in the trials that cured bubble boy disease for fifteen children, four in London and eleven in Paris.<sup>258</sup> The treatment had been permissible in France since 2000.<sup>259</sup> The gene therapy treatment for bubble boy disease involves using retroviruses to insert the healthy genes into blood stem cells to direct them to the T cells. The known risk of this particular method was that the retrovirus would transfer the gene to other cells as well, resulting in a disease causing mutation.<sup>260</sup> Leukemia, the disease contracted by two of the children treated with gene therapy for bubble boy disease, is where the blood cells, which naturally proliferate, proliferate out of control due to a mutation of the gene. Nonetheless, the serious effects of leukemia should not overshadow the fact that both these boys were successfully cured of bubble boy disease, which would have killed them within a couple years if left untreated. Furthermore, the other thirteen bubble boys treated with gene therapy benefited from the procedure without developing leukemia.

In August 2002, it did not actually come as a surprise to the doctors, the government, or the parents when a

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United States by 1997, but was delayed until at least three years and not in America, but instead in France. See "Gene Therapy: The First Halting Steps," THE JOURNEY BEGINS: THE CLINICAL TRIALS FOR ADA-SCID at [http://www.wrclarkbooks.com/downloads/healers\\_chapter.doc](http://www.wrclarkbooks.com/downloads/healers_chapter.doc).

<sup>258</sup> See "Miracle' Gene Therapy Trial Halted," NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878> ("A total of 15 patients, have been treated so far – 11 in Paris and four in London."). See also "Gene Therapy Causes Cancer in Mice," NEW SCIENTIST, April 18, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992186> ("So far, around 400 patients have received gene therapy in the UK alone, but only a few were treated with retroviruses. They include two 'bubble babies' otherwise condemned to living forever in germ-free 'bubbles' because their immune systems do not work.").

<sup>259</sup> See "Miracle' Gene Therapy Trial Halted," NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878> ("In 2000, a team lead by Alain Fisher at Necker Hospital, Paris, carried out the first gene therapy treatment, which replaced the faulty gene.").

<sup>260</sup> See "Gene Transfer," GENETICS AND PUBLIC POLICY CENTER at [http://www.dnapolicy.org/genetics/transfer.jhtml;\\$sessionid\\$4I4DCIQAACY4](http://www.dnapolicy.org/genetics/transfer.jhtml;$sessionid$4I4DCIQAACY4) ("Thus, a significant concern with gene transfer is that the introduced gene will integrate in the genome and cause interruption or disruption of other gene functions, causing mutation and possibly disease. This was considered a largely hypothetical concern until the recent occurrence of leukemia in a child who had gene transfer to treat a severe immune deficiency. While the transferred gene appeared to function and alleviate the immune deficiency, the appearance of the leukemia may have been due to the insertion of the transferred gene in yet another gene resulting in a disease causing mutation.").

child successfully treated for X-SCID with gene therapy developed leukemia. However, in response, France promptly halted the trials there as the FDA allowed the trials to continue in the United States.<sup>261</sup> Then, in January 2003, a second child treated in a French gene therapy trial developed a leukemia-like condition. Again, however, researchers anticipated this unfortunate consequence as a side effect from the science. The FDA immediately halted all gene therapy trials using retroviral vectors in blood stem cells as a response. At the time, there were two hundred gene-therapy trials under way, with sixty trials involving retroviruses, and twenty-seven trials using retroviruses to insert the genes into blood stem cells. Thus, the halted trials only represented fifteen percent of the gene therapy trials at the time. Yet, for the people affected by these fifteen percent of trials, the FDA decision is deadly harsh, overly risk-averse, and unfairly dictatorial. At the end of February 2003, the FDA's Biological Response Modifiers Advisory Committee ("BRMAC") met to discuss possible measures that could allow a number of retroviral gene therapy trials for treatment of life-threatening diseases to proceed with appropriate safeguards. The BRMAC recommended guidelines that would increase the benefit to risk ratio significantly. For instance, the BRMAC would deny gene therapy to X-SCID patients who had another treatment option, i.e., who had found matched<sup>262</sup> donors for marrow transplants. The BRMAC would permit X-SCID patients to undergo gene therapy if they could not find a matched donor, if their matched transplantation failed, and if their circumstances were otherwise so dire that gene therapy was the only remaining option. These recommendations would make gene therapy available only as a last recourse. However, today it is not available at all, because the FDA, over a year later, has not yet acted on the BRMAC recommendations from this meeting.<sup>263</sup> The January 14, 2003 FDA decision

<sup>261</sup>See "Miracle Gene Therapy Trial Halted," NEW SCIENTIST, October 3, 2002 at <http://www.newscientist.com/news/news.jsp?id=ns99992878> ("A 'miracle' gene therapy treatment for children suffering from the fatal 'bubble boy' disease has been halted in France, after one of the patients developed leukemia as a direct consequence of the treatment.").

<sup>262</sup>By "matched," the donor had HLA-identical bone marrow cells as the patient. HLA-identical means that the cell surfaces had the same HLA-antigens.

<sup>263</sup>See "Gene Therapy," HUMAN GENOME PROJECT INFORMATION at [http://www.ornl.gov/sci/techresources/Human\\_Genome/medicine/genetherap](http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherap) (noting that as of December 9, 2003, the "FDA had not yet to make a decision based on the discussions and advice of the BRMAC meeting"). See also "CBER Talkpapers," CENTER FOR BIOLOGICS EVALUATION AND RESEARCH at <http://www.fda.gov/cber/talkpapers.htm> (noting the FDA decision to halt the trials on January 14, 2003, and the BRMAC

to halt gene therapy trials, although affecting a very small percentage of the American population, calls the entire role of the FDA into question as overly risk-averse and authoritarian. Indeed, its own BRMAC recommended that the FDA allow gene therapy options in certain cases. The FDA's refusal to act upon these recommendations in one way or another, and thus take responsibility for its decision, instead of evading liability for the boys who die waiting for the FDA, is shameful.

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meeting on February 28, 2003, but without any update on the matter through March 26, 2004).

## IV. THE SOCIETY

### A. The Rights

The NIH established the Recombinant DNA Research Advisory Committee (“RAC”), and the FDA established the Center for Biologics Evaluation and Research (“CBER”), both to regulate gene therapy. Thus, gene therapy ended up being regulated twice, by two different federal organizations, and then within those two organizations, two separate committees that focused on gene therapy. Evidently, gene therapy deserves twice the scrutiny than any other treatment, despite the fact that gene therapy offers the only hope for many patients. Hence, the sad truth of the science working against bubble boy patients only becomes worse by the rigid FDA regulations working against bubble boy treatments.

Gene therapy passed multiple FDA tests before it even reached the human clinical trials that the FDA halted on January 14, 2003. As discussed earlier, leukemia was a known risk before the X-SCID gene therapy began trials. Nonetheless, the two cases of boys *cured* of X-SCID who developed leukemia-like symptoms still caused the FDA to halt the treatments responsible for the *cure*. The disease is deadly, but the FDA faces a duty to protect the American public. These two realities work against each other. Children are dying and parents are willing to do anything to save them. Children suffering from bubble boy disease are facing imminent death unless treated, and gene therapy is sometimes the only chance for life. Therapies are far from well understood and the FDA avoids the risks of the unknown. These conflicting interests are important, and yet at complete odds. Amongst these life and death decisions when each decision risks death, and no decision guarantees life, where do the rights of the parties involved lie?

The United States Supreme Court has found that the Constitution guarantees a right to privacy. In *Griswold v. Connecticut*,<sup>264</sup> the Supreme Court noted, “The association of people is not mentioned in the Constitution, nor in the Bill of Rights. The right to educate a child in a school of the parents’ choice – whether public or private or parochial – is also not mentioned. Nor is the right to study any particular subject or any foreign language. Yet the First Amendment has been construed to include certain of those rights.”<sup>265</sup> The Supreme Court found that “the First Amendment has a penumbra where privacy is protected from governmental intrusion.”<sup>266</sup> In applying this penumbra to affirm the privacy of marriage, the Court stated, “We deal with a privacy older than the bill of rights.”<sup>267</sup> This same statement applies to the privacy of life, self-preservation, and medical treatment, which is even older than the institution of marriage. The *Griswold* Court stated, “The foregoing cases suggest that specific guarantees in the Bill of Rights have penumbras, formed by emanations from those guarantees that help give them life and substance. Various guarantees create zones of privacy.”<sup>268</sup> No other right is more fundamental than the right to life. No other penumbra can give more life to this right than the right to medical treatment. The zone of privacy this right creates is the privacy to choose the medical treatment of gene therapy when there are no other treatment options. In *Eisenstadt v. Baird*,<sup>269</sup> the Court affirmed this right of privacy found in *Griswold*. The *Eisenstadt* Court stated, “If the right of privacy means anything, it is the right of the *individual*, married or single, to be free from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget a child.”<sup>270</sup> Similarly, the matter of gene therapy treatment, as a matter of life versus death, fundamentally affects an X-SCID patient.

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<sup>264</sup> *Griswold v. Connecticut*, 381 U.S. 479 (1965) (finding that the right to privacy guarantees the right to contraception).

<sup>265</sup> *Id.*

<sup>266</sup> *Id.*

<sup>267</sup> *Id.*

<sup>268</sup> *Id.*

<sup>269</sup> *Eisenstadt v. Baird*, 405 U.S. 438 (1972).

<sup>270</sup> *Id.*

The Supreme Court reaffirmed this right to privacy in *Roe v. Wade*.<sup>271</sup> The *Roe* Court stated, “The Constitution does not explicitly mention any right of privacy. [But] the Court has recognized that a right of personal privacy, or a guarantee of certain areas or zones of privacy, does exist under the Constitution.”<sup>272</sup> The Court has held that this right to privacy allows one to control one’s own body. In *Roe*, the Court found that this right extends to abortion, “because until the end of the first trimester mortality in abortion is less than mortality in normal childbirth.”<sup>273</sup> This analysis is particularly analogous to the gene therapy discussion, where the mortality of X-SCID patients is much higher without the right to this treatment than if this treatment were available. Both abortion and gene therapy are procedures that protect one’s mortality, but one is a rightful, undeniable choice, and one is an unlawful unavailable choice. Peculiarly, it is the choice that is unneeded by the availability of contraception that is legal, where the choice that is needed by the inescapable nature of genetic disorders is illegal. Peculiarly, the choice that, without, may come with a higher risk of mortality is legal, where the choice that, without, guarantees mortality, is illegal.

In deciding *Roe*, the Court noted, “This right of privacy, whether it be founded in the Fourteenth Amendment’s concept of personal liberty [as] we feel it is, [or] in the [Ninth Amendment], is broad enough to encompass a woman’s decision whether or not to terminate her pregnancy. The detriment that the State would impose upon the pregnant woman by denying this choice altogether is apparent. Specific and direct harm medically diagnosable even in early pregnancy may be [involved].”<sup>274</sup> Again, this statement can easily include gene therapy, where the specific harm that the government imposes with the halted trials is undeniable: boys die. The Court upheld “*Roe*’s essential holding”<sup>275</sup> in *Planned Parenthood of Southeastern*

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<sup>271</sup> *Roe v. Wade*, 410 U.S. 113 (1973).

<sup>272</sup> *Id.*

<sup>273</sup> *Id.*

<sup>274</sup> *Roe v. Wade*, 410 U.S. 113 (1973).

<sup>275</sup> *Planned Parenthood of Southeastern Penn. v. Casey*, 505 U.S. 838 (1992).



*Penn. v. Casey*.<sup>276</sup> The Court there stated, “[It] is tempting, as a means of curbing the discretion of federal judges, to suppose that liberty encompasses no more than those rights already guaranteed to the individual against federal interference by the express provisions of the first eight amendments to the Constitution. But of course this Court has never accepted that view.”<sup>277</sup> The Court noted, “It is a promise of the Constitution that there is a realm of personal liberty which the government may not enter.”<sup>278</sup> The Court then resolved, “[It] is settled now, as it was when the Court heard arguments in *Roe*, that the Constitution places limits on a State’s right to interfere with a person’s most basic decisions about family and parenthood, as well as bodily integrity.”<sup>279</sup>

The Supreme Court has also found a right to liberty, similar to the right of privacy, which also allows one to control one’s own body. For instance, *Cruzan v. Director, Missouri Dep’t of Health*<sup>280</sup> held the right to liberty guaranteed the right to refuse medical treatment, even if the treatment would be life-saving and to refuse it would be life-threatening. The Court has found *Cruzan* to hold, “The Due Process Clause guarantees more than fair process, and the ‘liberty’ it protects includes more than the absence of physical restraint. [The] Clause also provides heightened protection against government interference with certain fundamental rights and liberty interests.”<sup>281</sup> Along with *Maher v. Roe*,<sup>282</sup> where the Court found a right to medical treatment, the Court’s finding of rights to privacy, autonomy, personhood, liberty, life, and dignity support

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<sup>276</sup> *Id.*

<sup>277</sup> *Id.*

<sup>278</sup> *Id.*

<sup>279</sup> *Id.*

<sup>280</sup> *Cruzan v. Director, Missouri Dep’t of Health*, 497 U.S. 261 (1990) (finding, *inter alia*, that a person can refuse medical treatment eve if that refusal will cause death). “But when still a vibrant person Nancy had once remarked that she did not want to live ‘as a vegetable.’” *Id.* “[The] principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions.” *Id.* See also *Vacco v. Quill*, 521 U.S. 793 (1997) (noting that “[e]veryone, regardless of physical condition, is entitled, if competent, to refuse unwanted lifesaving medical treatment”); *Washington v. Glucksberg*, 521 U.S. 702 (1997) (citing *Cruzan* as support that “the Due Process Clause protects the traditional right to refuse unwanted lifesaving medical treatment”).

<sup>281</sup> *Washington v. Glucksberg*, 521 U.S. 702 (1997).

<sup>282</sup> *Maher v. Roe*, 432 U.S. 464 (1977) (upholding, *inter alia*, Connecticut’s use of Medicaid funds to reimburse women for the costs of medically necessary, including for reasons of mental health, abortions).

a Constitutional right to gene therapy when there are no other options. The *Roe* Court held, “[Where] certain ‘fundamental rights’ are involved, the Court has held that regulation limiting these rights may be justified only by a ‘compelling state interest,’ and that legislative enactments must be narrowly drawn to express only the legitimate state interests at stake.”<sup>283</sup> What is the compelling state interest in denying medical treatment, in denying control over one’s own body, in denying the right to privacy, in the FDA decision that denies the option of gene therapy? Although overruled by the Supreme Court, the Tenth Circuit made a powerful argument, “[W]hat can ‘generally recognized’ as ‘safe and effective’ mean as to such persons who are so fatally stricken with a disease for which there is no known cure?”<sup>284</sup> The concern of the Supreme Court in overruling this decision was in finding that there is “no special provision for drugs used to treat terminally ill patients.”<sup>285</sup> However, these patients are not arguing for a special right for terminally ill patients any more than abortion gives a special right for pregnant women or the right to refuse medical treatment gives a special right for those in need of medical treatment. Instead, the Supreme Court should view it as a right for all to choose riskier treatments when death is imminent and there are no alternate treatments. Furthermore, the Tenth Circuit decision articulates that the compelling state interest in protecting human life,<sup>286</sup> and in thus prohibiting life-threatening treatments, cannot be applied to a person whose only chance of survival is the life-threatening treatment.

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<sup>283</sup> *Roe v. Wade*, 410 U.S. 113 (1973).

<sup>284</sup> *Rutherford v. United States*, 582 F.2d 1234, 1237 (10th Cir. 1978).

<sup>285</sup> *Rutherford v. United States*, 442 U.S. 544 (1979).

<sup>286</sup> See, e.g., *Roe v. Wade*, 410 U.S. 113 (1973) (“We repeat, however, that the State does have an important and legitimate interest in preserving and protecting the health of the pregnant woman [and] that it has still *another* important and legitimate interest in protecting the potentiality of human life.”).

## B. The Lives

The FDA admittedly has a congressional mandate to regulate gene therapy and to protect the American public. However, the proper interpretation of this mandate must be different in cases involving rare life-threatening diseases. Under the Supreme Court rulings above, the FDA should adopt less rigid regulations, allow for greater personal autonomy by permitting high-risk treatment options when there are no other options, and the disease is fatal. A governmental tolerance for high-risk treatments in cases of X-SCID makes legal, financial, and ethical sense, since the United States Constitution guarantees individual liberty, the resources of the FDA are limited, and the alternative for these children is only death.

The FDA mandate should include a duty to protect American rights, as well as American lives. Thus, in fatal diseases, especially where there are no other options, the FDA regulations must be more flexible, to acknowledge that the compelling state interest of protecting life changes in those cases. The FDA mandate should include a duty to inform and educate patients to help patients make their constitutionally protected choice. The FDA mandate would continue to include a duty to protect lives. For high-risk treatments of life-threatening diseases, the FDA could require that the patients sign a contract that binds patients and waives claims for damages.<sup>287</sup> In the case of X-SCID gene therapy treatments, the FDA could adopt the standards recommended by the Biological Response Modifiers Advisory Committee (“BRMAC”). The FDA could limit potential gene therapy candidates to patients who do not have a donor match for a bone marrow transplant, have a high likelihood of contracting graft versus host disease (“GVHD”), or have had an unsuccessful transplant.

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<sup>287</sup>This option is not currently available under the Investigation New Drug (“IND”) process for drugs that are currently in the clinical trial phase that treat fatal diseases.

Finally, the FDA could focus more, especially with bubble boy disease, on early diagnosis. “‘This once-fatal disease should be now seen as a pediatric emergency, a condition that needs immediate diagnosis and treatment,’ says Dr. Rebecca Buckley, chief of Duke’s division of pediatric allergy and immunology.”<sup>288</sup> SCID patients would have a higher chance of survival with an early diagnosis, before the disease reached advanced stages. “The transplant needs to be done before the onset of opportunistic infection, she explained, and in the first few weeks of the baby’s life, when the donor marrow takes hold quickest. Waiting until after the first four weeks of life increases the risk of infection, as well as slowing the development of immunity from the donor transplant.”<sup>289</sup> Indeed, researchers recommend testing newborn babies, because even a month-old baby has an increased risk in the transplant than a newborn. “Early diagnosis of SCID is rare because doctors do not routinely perform a test in newborns to count white blood cells. Such a blood test could pick up children with SCID as well as those with other serious immune deficiencies that would not be apparent until the child developed an infection.”<sup>290</sup> Doctors argue for early diagnosis to give more time to find a matched transplant donor, to have a chance to do the transplant while the child is still healthy, and to allow for less costly procedures. “‘A simple blood test could allow us to treat, and most likely cure, SCID in an infant at a reasonable cost. If found later, less effective treatment can run into the millions.’ Buckley states, ‘What we’re saying is that essentially every baby with SCID could be cured if diagnosed early enough. SCID should be considered a pediatric emergency.’”<sup>291</sup>

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<sup>288</sup> “Early Marrow Transplant May be Key to ‘Bubble Boy’ Disease Cure,” DOCTOR’S GUIDE, May 5, 1997 at <http://www.pslgroup.com/dg/25666.htm>.

<sup>289</sup> *Id.*

<sup>290</sup> *Id.*

<sup>291</sup> *Id.*

## V. CONCLUSION

In conclusion, the American public has a legal right to choose the best treatment for life-threatening diseases when there are no available risk-free treatments and there is a guarantee of an early death without any treatment. In the case of rare fatal diseases, the individual patient is in the best position to research options, and make decisions based upon those options. The overly risk-averse nature of the FDA may violate constitutional rights and American values.

The FDA can implement less rigid regulations for high-risk treatments involving life-threatening diseases without threatening its authority in protecting the American public. Although the FDA cannot be responsible for the risks of gene therapy when those risks are well understood, the FDA can bind patients who choose risky procedures. These contracts could include clauses that waive the patient's rights to file a claim later against the hospitals, doctors, and researchers for liability or damages.<sup>292</sup> Furthermore, the FDA could limit potential gene-therapy candidates to patients who do not have a donor match for a bone marrow transplant, or have a high likelihood of contracting graft versus host disease ("GVHD").

American values cherish individual freedoms of privacy, human dignity, and autonomy. Thus, it is imperative for the FDA to change its standard procedures to fall in line with those values. In an effort to protect society from itself, the rolling wheels of the legal system too often enact paternal laws that conflict with these values. Unfortunately, while American may possess a model system, it still fails to check and balance laws as quickly as they can be passed.

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<sup>292</sup>Under the Federal Tort and Claims Act, patients cannot sue the FDA, but this new waiver would similarly protect hospitals, doctors, and researchers of dangerous treatments for rare and fatal diseases, like X-SCID.

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# ACRONYMS

ADA-SCID = adenosine deaminase severe combined immunodeficiency

AIDS = acquired immunodeficiency syndrome

BRMAC = Biological Response Modifiers Advisory Committee

CBER = Center for Biologics Evaluation and Research

FDA = Food and Drug Administration

GVHD = graft versus host disease

HIV = human immunodeficiency virus

IND = investigational new drugs

IRB = institutional review board

NIH = National Institutes of Health

RAC = Recombinant DNA Research Advisory Committee

SCID = severe combined immunodeficiency

X-SCID = X-linked severe combined immunodeficiency